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STUDIES ON THE VELOCITY OF BLOOD FLOW

I THE METHOD UTILIZED[1]

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An adequate flow of blood to the tissues implies two things In the first place an adequate amount of blood must be expelled from the heart per unit of time In the second place this blood must be transported to the site of utilization at an adequate speed The former aspect of the circulation, the minute volume output, has received considerable study The second aspect, the velocity of blood flow, has not Nevertheless, discussions of the probable velocity and its significance in maintaining the physiological integrity of the body have frequently been reported

HISTORICAL RÉSUMÉ OF METHODS EMPLOYED IN STUDYING THE VELOCITY OF BLOOD FLOW

With the discovery by Harvey in 1628 (1) of the movement of blood in a circuit, the problem of the velocity at which the blood flows first presented itself Not until 1733, however, when Stephen Hales (2) published his penetrating inquiries was the question of the velocity of blood flow discussed in quantitative terms His grasp of the essentials of the problem was extraordinary From his estimation of the capacity of the left ventricle, the diameter of the base of the aorta, and the pulse rate he computed the velocity of blood flow in the aorta of the horse.

The problem of the velocity of blood flow received its next impetus in 1827, when Eduard Hering (3) measured the velocity of blood flow by injecting a solution of potassium ferrocyanide at one point and

[1] This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Disease.

determining its time of arrival in the blood at another point in the vascular circuit by testing the samples of withdrawn blood for prussian blue He measured in this way the circulation time from the right to the left external jugular vein

In 1850, Volkman (4) constructed the haemodromometer, a pendulum device which gauged the velocity of blood flow by recording the movement of a pendulum placed in the lumen of a blood vessel The inertia of the instrument was sufficient to distort the results But aside from this defect the obstruction imposed by the instrument to the onward flow of blood must have altered the velocity

The haemotachometer designed by Vierordt (5) was a distinct improvement His method resembled Hering's, but whereas Hering's observations were confined solely to horses, Vierordt extended his to rabbits, hedgehogs, squirrels, cats, dogs, ducks, cocks and geese Actually, he observed the time necessary for the fastest particle of blood to traverse various paths From these data he attempted to estimate the mean velocity (page 119) Vierordt improved Hering's method by affixing a number of cups to a disc (page 56), which was rotated at a uniform and known rate In each of the cups he collected samples of blood drawn at intervals of one second

In the latter part of the nineteenth century, there were repeated attempts to estimate the velocity of the blood in the arteries and veins by means of Cybulski's photohaemotachometer and O Frank's differential manometer The insertion of such devices into the blood stream demanded much manipulation and introduced so many extraneous physical factors that the results were difficult of accurate interpretation, and therefore failed to clarify the problem

More fruitful was the approach of G N Stewart (6) who studied the circulation time by injecting a hypertonic solution of sodium chloride into one jugular vein, and by ascertaining its time of arrival in another vessel The time of arrival was signalled by a change in the electrical conductivity of the blood in the vessel, which was placed between two non-polarizable electrodes He also utilized methylene blue injections observing by transillumination the time at which the dye appeared in the common carotid artery He studied the circulation times of many pathways in various animals and also studied the circulation times of individual organs

In 1922, E Koch (7) presented his measurements of the circulation time in man in both normal and pathological states His method consisted of the injection of 1 0 cc. of a 1 6 per cent solution of fluorescein into the cubital vein of one arm and then obtaining samples of blood at five second intervals from the cubital vein of the other arm The dye, therefore, traversed the veins to the right ventricle, the lung circulation to the left ventricle, the aorta, the arteries of the arm, the peripheral capillaries of the arm, and then finally, the vein from which the blood was collected His results will be discussed later It should be noted, however, that withdrawal of blood is feasible only from the cubital vein In order to determine the time of arrival of such a dyestuff, it is necessary that a constant stream of blood flow from the arm through the needle to the collecting tubes The formation of clots, the inaccessibility of veins, alteration of flow by the introduction of the needle into the vein, all necessarily interfere with the trustworthiness of such a method

Because of the inaccuracies and limitations of previous methods, we felt the necessity of developing a more satisfactory approach to this fundamental problem

Theoretically the most desirable measurement of the velocity of blood flow consists in establishing the separate velocities of each minute portion of the blood along the many separate paths When one considers that the innumerable vessels in the body are constantly changing in size and elasticity and that the blood is a suspension of corpuscles in a fluid medium, the impossibility of fulfilling the ideal requirements becomes obvious The problem is further complicated, any mean velocity measurements which depend on the insertion of a mechanical device into the blood stream defeats its ends and can therefore, not be considered for clinical application The most feasible method appears to be the injection of some substance at one point in the body, and the measurement of the time of its arrival at another point Consideration of the problem shows that the substance to be used must fulfill the following requirements

1 The substance must not be toxic in the amounts utilized Toxicity is of course a relative quality, for any substance, if given in sufficiently large amounts, may bring about grave consequences

2 The substance should not be present previously in the body

Estimation of additional amounts of substances already within the body is always subject to error Weber's law, moreover, is applicable According to this law, the increase of stimulus necessary to produce an appreciable increase in sensation must always bear the same ratio to the whole stimulus If, accordingly, a substance were already present, greater amounts of that substance must be injected to produce appreciable changes at the point of detection

3 The substance must not in any way disturb the very phenomena under investigation Toxicity would introduce such an error The introduction of hypertonic salt solution would also cause an error for it would alter the blood volume, vary the speed of blood flow, and thereby modify the very phenomenon under investigation

4 It is desirable that the substance disappear from the body with sufficient rapidity to allow of repeated measurements

5 The substance must be readily detectable in minute amounts Were this impossible, varying dilutions of the substance would be all the more likely to produce correspondingly variable results

Initial attempts were made in animals to test the usefulness of various substances We injected intravenously salts such as those of lithium and strontium, and examined spectroscopically drops of blood from various parts of the body The results were unsatisfactory

The use of the active deposit of radium (or radium C) had yielded a method which fulfills the foregoing criteria and has proved entirely satisfactory [2]

The method consists of the injection of the active deposit of radium at one point in the body, and the detection of its time of arrival at another point The active deposit is particularly suited to the purpose because of the following properties In the first place, it is nontoxic in the amounts necessary for the purpose Quick and Duffy (8) at the Memorial Hospital in New York in studying the possible therapeutic effects of radium C in patients with advanced generalized carcinomatosis gave repeatedly intravenous injections of 50, and 75 millicuries without any consequent ill effects They studied the urine for signs of renal irritation, and the blood for evidence of nitrogen retention, without noting any untoward effects No significant

[2] In a forthcoming paper, we intend to describe the method of preparation of radium C

changes were noted in the red blood cell count or hemoglobin Our own experiments on animals and, as will appear below, our subsequent study of the effect of radium C in ourselves and in patients has uniformly showed an absence of any objective or subjective ill effects In a few patients with generalized carcinomatosis large amounts of radium C were administered, the amount necessary, however, for a measurement is only one to four millicuries

Active deposit fulfills the other requirements previously mentioned It is not present normally in the body The injection of radium C into animals and later into human beings has shown a uniform absence

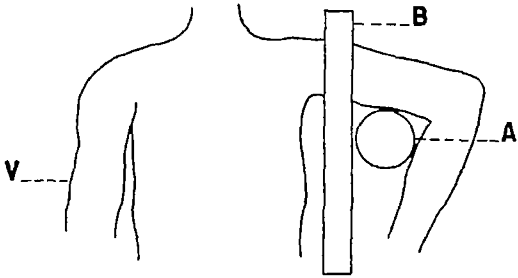

FIG 1 DIAGRAM OF RELATION OF THE LEAD SHIELD AND THE DETECTING DEVICE TO THE PATIENT

A, detecting device, *B*, lead shield through which the left arm passes, *V*, right arm.

of any discernible alterations in the blood pressure or the ventricular rate or the ventricular rhythm The properties of the active deposit of radium are such moreover, that observations can be repeated after approximately three hours, inasmuch as the active deposit decomposes to within 3 per cent of its initial value at the end of that time As to its detectability in small amounts, the active deposit leaves nothing to be desired since the presence of a single atom can be detected

The active deposit lends itself particularly to the purpose of measuring the velocity of blood flow because of its radiation, for, being a member of the radium family, it gives out penetrating radiation in

the form of beta particles or electrons, and gamma rays which are comparable to hard x-rays These radiations penetrate ordinary materials such as tissues and air, but can be stopped by lead If the active deposit of radium is injected into the vein of one arm (fig 1), it gives off radiation as it is carried up the arm to the right side of the heart and thence through the lungs to the left side of the heart The lead shield *B*, prevents the radiation from reaching the detecting device *A* As soon as the radium active deposit reaches the arterial vessels of the arm beyond the lead block, the radiations are no longer separated from the detector *A*, by lead Instead, they penetrate the tissues, traverse the air, and enter the detecting device, where they appear as definite white streaks

DESCRIPTION OF THE APPARATUS

1 The detecting device

To secure a suitable detecting device proved to be a formidable undertaking The usefulness of instruments for detecting minute amounts of radioactive substances depends on their ability to detect the characteristic beta and gamma radiations which are emitted from within the atom These radiations cause ionization of any gas they traverse Conversely, under suitable conditions, the onset of ionization in a gas can therefore be assumed to indicate the presence of the radiation of a member of a radioactive series

The use of an electroscope as a detector was attended with great difficulties Perfectly satisfactory shielding of the electroscope from the radiations of the active deposit as it coursed through the body was impracticable Morever, the precise instant at which the radium active deposit arrived was extraordinarly difficult to ascertain by this device

Kovarik's modification of the Geiger counting chamber was likewise tested (9) The necessity of a source of constant high potential, the instability of the steel needle electrode, and the relatively high number of spontaneous discharges discouraged the choice of this mode of detection

We also attempted to use parallel plate ionization chambers We found, however, that the large electrical capacity of the plates reduced

the sensitivity of the ionization chambers, even when we used low pressures and introduced various vapors to obtain the greatest possible amount of ionization by collision

The use of a cloud chamber of the C T R Wilson type (10) approached more closely our requirements In principle this apparatus consists of an air tight chamber saturated with water vapor At the bottom of the chamber is a piston which falls periodically, and in so doing produces an adiabatic expansion of the enclosed volume of air and water vapor The vapor is cooled to such an extent by this expansion that it becomes critically supersaturated In this state, the vapor condenses in the form of minute droplets upon any small particles such as dust, which are suspended in the gas If no dust particles are present, the water vapor condenses in minute droplets upon any electrically charged bodies such as ionized molecules If, for instance, a gamma ray or beta particle should traverse the chamber and create an ionized path, while the chamber is in the condition of critical supersaturation, the water vapor would condense as minute droplets along the ionized path With proper illumination, this ionized path appears as a white streak Unfortunately, a constant state of supersaturation can not be maintained, but by the use of a reciprocating piston device of the Shimizu type (11), the chamber can be rendered periodically susceptible to the formation of droplets along any ionized path The critical degree of supersaturation, therefore, is attained on each descent of the piston

The detecting device which we finally adapted from that of C T R Wilson may be represented diagramatically (fig 2) Letter *F* is a brass cylinder into which a duralumin piston, *D*, is accurately fitted This piston is connected below to a shaft, *R*, which is moved up and down by a cam, *P* Every revolution of the cam *P* causes the piston, *D*, to drop suddenly from a high to a low position The top and the bottom positions and therefore the extent of the fall are all adjustable by the bearing *S* This device is of considerable importance, for the degree of vapor supersaturation required is a critical one. It is dependent on variable conditions such as room temperature and the amount of water vapor initially present in the chamber Once the adjustments are made, however, by means of varying *S*, no further manipulations are necessary during the time of an experiment

Upon the top of a cylinder is screwed the chamber consisting of a threaded brass collar, *B*, celluloid ring, *C*, and glass top plate *A*. The celluloid ring consists of a strip of celluloid 0.005 inch in thickness, the ends of which are stuck together with amyl acetate. By means of rosin it is rigidly set into a groove in the brass collar below, and into a corresponding groove in the glass plate above. The rosin must

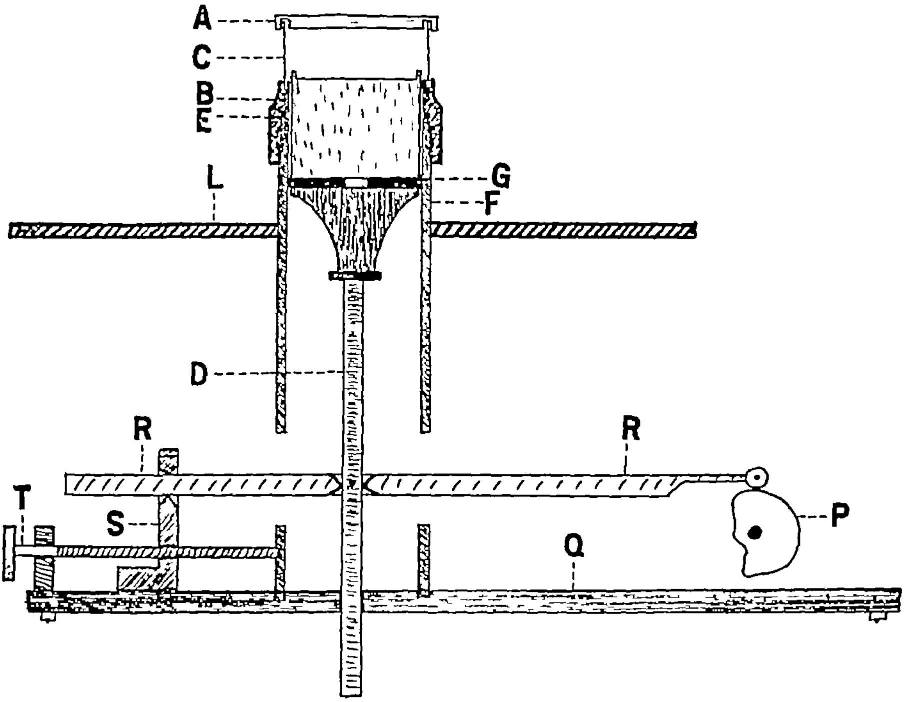

FIG. 2. DIAGRAM OF DETECTING DEVICE

A, glass top plate, *B*, threaded brass collar, *C*, celluloid ring, *D*, duralumin piston, *E*, rubber washer, *F*, brass cylinder, *G*, leather washer, *P*, cam, *Q*, steel bottom plate, *R*, duralumin shaft, *S*, support and bearing for shaft, *T*, adjusting screw, *L*, shelf for arm rest

be heated to a temperature of 110° to 130°C. and it must be free of air bubbles.

The top of the piston and the bottom of the cover glass are coated with gelatin. The gelatin covering the piston is blackened with India ink. The gelatin covering the top glass plate contains a small amount of copper sulphate and can therefore, be used to establish an electri-

cally negative charge The charge passes into the chamber by means of a tongue of lead foil, leading to a thin ring imbedded in the copper sulphate gelatin The charge established on the top plate consists of about minus fifty volts It serves to dispel the tracks formed at each descent of the piston In this way the chamber is cleared for the new tracks of the next expansion The piston is at ground potential The charge on the top plate is applied during only a portion of the upstroke During the rest of the time the top plate is grounded The regulation of the charge on the top plate is accomplished by means of an adjustable commutator operated from another cam, not shown in the diagram but concentric with the cam, *P*

The cycle of events is therefore as follows During the downstroke of the piston the gas in the chamber is suddenly expanded and becomes supersaturated for an instant If, during this instant, any primary or secondary beta particles are travelling through the chamber, the water vapor condenses along that path and when properly illuminated appears as thin, white streaks The streaks or tracks settle slowly under gravity, but before they have moved far the piston returns to its former high position and the gas is again at its initial volume Part of the drops immediately evaporate The others are swept to the top of the piston below by the repelling force of the negative electric charge on the top plate The chamber is again clear and ready for another expansion

The instrument may be operated at any rate up to three or five expansions per second, but about one per second has proven most satisfactory The moving parts are placed below the cylinder head so that the patient's arm may be conveniently laid upon the iron plate, *L*, and brought against the thin celluloid rim *C*

In the actual observations we have placed the detecting device within the bend of the elbow, so that the ionization chamber is exposed to the radiation from the brachial artery and its branches The arm of the patient passes through a lead block 8 cm in thickness, which serves to prevent radiations from the rest of the body from reaching the detector

PROCEDURE OF THE MEASUREMENTS

Sodium chloride is exposed to radium emanation for an appropriate length of time, during which radium C is deposited upon the salt

The method utilized is that described by Theis and Bagg (12) The sodium chloride is then dissolved in sterile distilled water and its radioactivity measured by means of a gamma ray electroscope The volume of the solution, which is contained in the syringe is usually about 0 5 cc

The measurement of the velocity of blood flow is made under basal metabolic conditions, no food being taken by the patient after supper on the preceding evening The patient lies down in bed and rests for at least twenty minutes The left arm is passed through the lead block and arranged around the cylinder of the cloud chamber The active deposit is not injected for at least twenty minutes after it has been removed from exposure to the emanation to allow the alpha ray activity to decay to four per cent of its initial activity (13) The cubital vein of the right arm is entered with a sharp needle to which is attached a three-way stopcock A small amount of blood is withdrawn in order to be certain that the needle lies free within the vein The stopcock is then turned so that the needle communicates with a manometer filled with a solution of sodium citrate The level of the top of the sodium citrate in the manometer is then compared with the level of the right auricle The details of the measurement of venous pressure are practically those published originally by Moritz and Tabora (14)

The syringe into which the blood was drawn is replaced by one containing the radium active deposit The stopcock is then turned and the 0 5 cc solution containing a minute volume of active deposit is quickly injected into the vein The injection time is always less than one second As the active deposit courses through the body an occasional track is visible within the cloud chamber With the arrival of active deposit within the arterial vessels of the arm, beta particles and gamma rays pass through the tissues of the arm, traverse the thin celluloid rim, enter the cloud chamber, and there become visible Instead of an occasional track, at least two or more tracks are visible at succesive expansions The time of arrival of the active deposit in the arterial vessels of the left arm is registered by means of a stop watch The difference between the time of injection and the time of arrival gives the velocity of blood flow between the two points The amount of active deposit utilized for a determination has been from

1 to 6 millicuries On theoretical grounds it is difficult to conceive of such amounts causing any toxic effects In practice we have verified the theoretical expectation

RESULTS

The primary purpose of the preliminary measurements was rather to test the method than to gain additional knowledge of the circulation The velocity of blood flow (measurement numbers 1, 2, 3, 4, 5, 6)

TABLE 1

Number	Date	Diagnosis	Millicuries injected	Circulation time
2	February 28 1925	Carcinoma of esophagus	52	18
5	March 2 1925	Metastatic carcinoma of liver	17	20
10	March 2 1925	Chronic myocarditis	18	32
3	March 3 1925	Carcinoma of stomach	33	18
9	March 3 1925	Jaundice, bradycardia	5	30
8	August 22 1925	Emphysema	35	28
7	August 22 1925	Emphysema	5	25
13	August 28 1925	Auricular fibrillation	38	55
12	September 1 1925	Auricular fibrillation	4	53
1	August 28 1925	Chronic arthritis	2	15
4	August 29 1925	Normal	2	18
6	September 1 1925	Normal	1	21
14	August 29 1925	Cardiac decompensation	4	65
15	September 1 1925	Chronic myocarditis		
		Cardiac decompensation	2	71
11	September 1 1925	Auricular fibrillation		
		Cardiac decompensation	7	50

(table 1) was studied in patients in whom the cardio-respiratory system was normal The time required for the substance to flow from one arm to the other arm was found to be from fifteen to twenty-one seconds These results are in contrast with the velocities recorded in three patients who showed signs or symptoms of cardiac decompensation In these patients (numbers 12, 14 and 11), the times noted 53, 65 and 50 seconds clearly belong to a different order

Observations were repeated in the same individuals to test the reliability of the method Measurements 7 and 8, 4 and 6, 12 and 13 all show agreement within three seconds Of particular interest are

numbers 7 and 8, for the amount of deposit utilized in the first is sevenfold that injected for the second measurement

In all these patients the urine was carefully examined immediately before and immediately after injection, and uniformly failed to show any signs of renal irritation No anemia followed the injection of radium C in the amounts used

CONCLUSIONS

A new method is presented for the measurement of the velocity of blood flow in man The active deposit of radium is injected into the antecubital vein of one arm and its time of arrival in the other arm is detected by means of a modified C T R Wilson cloud chamber device The advantages of the method are as follows

1 The volume of fluid injected is very small

2 The substance injected is non-toxic in the amounts utilized

3 The presence of extraordinarily minute amounts of the substance can be detected with certainty

4 The radiations by traversing the tissues of the arm automatically indicate the time of arrival of the active deposit

5 No withdrawal of blood is necessary

6 The method is objective requiring no cooperation on the part of the patient

7 The method gives a quantitative estimate of a fundamental aspect of the circulation

We wish to express our appreciation to Dr Francis W Peabody for his constant advice and encouragement

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STUDIES ON THE VELOCITY OF BLOOD FLOW

II THE VELOCITY OF BLOOD FLOW IN NORMAL RESTING INDIVIDUALS, AND A CRITIQUE OF THE METHOD USED[1]

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INTRODUCTION AND HISTORICAL RESUMÉ OF PREVIOUS MEASUREMENTS OF THE VELOCITY OF BLOOD FLOW

Since the beginning of experimental physiology the velocity of blood flow has attracted the interest of students of the circulation Harvey (1) in 1628 stated "   the circuit of the blood is accomplished now more rapidly, now more slowly according to the temperament, age, etc of the individual, to external and internal circumstances, to naturals and non-naturals,—sleep, rest, food, exercise, affections of the mind and the like" But the first physiologist who attempted actually to measure the velocity of blood flow was Stephen Hales (2) He estimated the velocity of the blood flow in the aorta of the horse to be 1734 9 feet per hour (page 21), and in man 8952 0 feet per hour (page 47) By direct microscopic observation of the capillaries of the frog's lungs, he estimated the speed to be 0 1 of an inch in $\frac{1}{1\frac{1}{2}}$ second, or about 50 inches per second He believed the velocity of blood flow in the capillaries of the abdominal muscles to be $\frac{1}{13}$ that observed in the lung Since then, numerous investigators have made measurements

Eduard Hering (3) in 1829, studied the circulation time of the horse and found that it required 26 2 seconds for a particle to pass from jugular vein to jugular vein

An extensive study was made by Karl Vierordt (4) who found that the circulation times over analogous paths in different animals bore

[1] This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases

an inverse relation to their size, that is to say, the smaller the animal, the greater the velocity. He also observed that the circulation times were related to the pulse rate, in that, regardless of the size of the animal the mean circulation time of the path from the external jugular vein back to the external jugular vein corresponded to the time of twenty-six to twenty-nine heart beats. From this observation he made the inference that in man the circulation time from one external jugular vein back to an external jugular vein occupied 23.1 seconds if the heart rate were 72.

A new interest was taken in the subject when G. N. Stewart (5) began in 1894 to publish his observations on the circulation times of various pathways of the animal body. In dogs he found that from the right ventricle to the aorta, 1.7 to 8 seconds were required according to the size of the dogs used.

The only attempt to measure the circulation time in man was made by Koch (6). He injected fluorescein into the cubital vein of one arm, and observed the time of arrival of the dye in the vein of the opposite elbow. In fifty-one normal male persons between the ages of fifteen and seventy-nine, he found the average to be 20.4 seconds. We attempted to confirm Koch's results but found it difficult to obtain satisfactory measurements due to lack of cooperation on the part of the patients, to the variability of flow through the needle, and to the tendency of the blood to clot. The recognition of the first trace of fluorescence is often attended with difficulty. In spite of its drawbacks, we utilized the fluorescein method in order to confirm our results with those gained by another method.

In order to obviate the disadvantages of the previous methods, we devised and utilized a method outlined in a preceding communication. This study presents a critique of our method and the results of fifty-six measurements of the velocity of blood flow in fifty-three normal male individuals. The velocity was ascertained by measuring the time required for the active deposit of radium to flow from the cubital vein of one arm to the arterial vessels about the elbow of the other arm.

CRITIQUE OF THE METHOD

We have felt the trustworthiness of a method is proportional to the small number of underlying assumptions. We have therefore under-

taken to verify by direct observation every step of our procedure, and to control as far as possible the variable factors The chief precautions we have observed are the following

I Preparation of the active deposit

The active deposit is collected on a platinum needle electrode.[2] The needle is moistened with 10 per cent hydrochloric acid in a capillary tube, and concentrated sodium hydroxid is then added until the solution is neutral to phenol red This procedure is performed in a glass capillary tube from which the fluid is drawn up into a 1 cc tuberculin syringe, and from this injected into an arm vein The effect of an increase in volume of the blood stream can be disregarded since the volume injected ranges from 0 1 to 0 2 cc So minute an amount of hypertonic solution can exert no effect of physiological consequence

II Injection of the active deposit

The injection is performed in the following manner A tourniquet is applied for as short a time as possible, while a sharp needle connected to a three way stopcock is inserted into the lumen of the vein The tourniquet is then removed By connecting the needle to a glass manometer containing sodium citrate, the venous pressure is measured according to the method of Moritz and Tabora The rapid descent of the citrate solution in the manometer tube, and the presence of the respiratory undulations indicate that the needle communicates freely with the vein The stopcock is then turned and the active deposit injected The volume is so small that only a fraction of a second is required for the injection The duration of the injection, is a small fraction of the time which elapses between that of injection and that of arrival at the opposite arm, and constitutes therefore, a negligible error only of not more than 0 5 second Three to five minutes elapse from the time the tourniquet is removed until the active deposit of radium is injected Any circulatory changes caused by the application of the tourniquet are therefore reduced to a minimum

A complete description of this procedure will appear in a forthcoming communication

III The condition of the patient

All the patients studied were convalescent from diseases neither cardio-respiratory, nor metabolic, nor haemic in nature Physical examination at the time of the test revealed no cardio-respiratory abnormalities Practically all the observations were made under basal conditions, twelve to fourteen hours having elapsed since the last meal The patient always rested in bed at least twenty minutes beforehand By explanation and by obtaining the patient's consent and cooperation, apprehension was obviated The temperature, the pulse rate and the rate of respiration were noted The apparatus was always set in motion for a short period before the onset of the observation to accustom the patient to the unusual environment The pulse was counted again immediately after the measurement, and was seldom found to have changed more than five beats Several persons showed a persistently high ventricular rate before and after the test

IV Site of the active deposit of radium at the time of the onset of the ionization effect

It is, of course, of fundamental importance to be certain that the onset of the disturbance in the cloud ionization chamber is due to radium C in the vessels of that portion of the arm immediately adjacent to the celluloid collar, and not to its presence elsewhere, as it courses through the other vessels of the body To protect the chamber, a lead block 80 to 220 mm thick was used which absorbed the radiations which issued from the approaching radium C According to Rutherford (7) lead of this thickness should, theoretically, more than suffice Practically, if the equivalent of the entire amount injected was placed behind the lead block, the small amount of penetrating radiation reaching the cloud chamber was negligible The disturbance set up in the chamber by the short secondary low velocity beta rays consists of short fuzzy tracks which are in striking contrast to the bundles of straight beta ray tracks that appear when the active deposit reaches the arterial vessels of the arm about the celluloid collar The C T R Wilson type of apparatus[3] enables one, moreover, to judge the direction of the tracks, and so to gain an idea of its source

[3] The apparatus is described in a preceding communication

A demonstration even more conclusive of the fact that the cloud effect was due to active deposit in the vessels of the arm was obtained in every experiment by directing the patient to withdraw his arm from the chamber and to place it behind the lead shield immediately upon the conclusion of the velocity measurement At this moment the body was still giving out radiation The striking disappearance of the straight beta ray tracks showed that the cloud effect had not been due to radium C present in the chest or in the rest of the body

V Localization of the source of the cloud effect in the blood vessels of the arm

The above facts establish that the cloud effect is due to active deposit in the vessels of the arm placed about the detecting chamber One might still question, however, whether at the time of the appearance of the cloud, the active deposit was in the arteries, in the capillaries, or in the veins Inability to answer this question would not necessarily invalidate the use of the method as a means of securing measurements for purely comparative purposes The significance of the method would, however, be greatly heightened if one could establish the site of the active deposit at the time of the onset of the disturbance in the ionization chamber From the point of view of theoretical physics, it is almost certain that the onset of the cloud effect is due to the entry of the blood containing active deposit into the larger arteries about the elbow The cloud chamber records the path traversed by a single electron, so that a few atoms of active deposit should be sufficient to produce the cloud effect

To secure direct evidence upon this question, the following procedures were carried out The arm-to arm velocities of a group of patients were ascertained according to the usual procedure The values obtained are shown in table 1, column 5 Subsequent measurements were also made on these patients by injecting 2 cc of a 1 5 per cent solution of fluorescein to which had been added 2 to 4 millicuries of the active deposit We have already described the limitations in the use of fluorescein, but it affords nevertheless the only available means of verifying certain aspects of our method The solution was injected into the cubital vein of the right arm, while a large needle was inserted into the cubital vein of the other arm

Samples of blood were collected every three or five seconds Each sample of blood was tested for the presence of active deposit and for the presence of fluorescein The observations were made independently by different observers The presence or absence of the substances was ascertained separately and checked without knowledge of the sequence in which the blood had been collected The first specimen of blood in which the dye or active deposit was detected, is named and recorded according to the length of time after the intravenous injection of the solution The time of the injection is

TABLE 1

Comparison of the circulation times obtained by the radium active deposit method, and by testing the venous blood directly for the presence of fluorescein and for the presence of radium active deposit

Number of measurement	Name	Age	Diagnosis	Circulation time		
				Radium active deposit method	Fluorescein test	Direct radium active deposit test
				seconds	*seconds*	*seconds*
34	S F	19	Normal	15	25–30	
36	T G	78	Myocardial degeneration	48	60–65	
37	P S	37	Malignant	25	30–35	
49	R M	66	Myocardial degeneration	26	35–40	
58	T M	64	Arterio sclerosis	29	45	45
69	D M	53	Auricular fibrillation	42	45–50	45–50
71	T M	53	Auricular fibrillation	25	30–35	30–35

regarded as zero, this assumption introducing an error of not more than two seconds

Certain of the results are significant First, the cloud effect, according to the usual procedure, took place in every instance at least five seconds earlier than the appearance of fluorescein or active deposit in the blood drawn from the antecubital vein This signifies that the appearance time of the active deposit of radium as noted by the emergent rays from the tissues of the arm is always observed at least some five seconds before it reaches the corresponding vein of that arm The presence of radium C or fluorescein in a twenty-five to thirty second sample may, of course be due to the arrival of these substances

during the first, or during the last second of the collection so that these results cannot be interpreted too precisely The fact that there was at least a five-second difference is of considerable importance, however The time for blood to course from the arterial to the venous side of the arm is probably not more than five seconds We therefore believe these findings to be further evidence that the onset of the cloud effect is due to radiation from active deposit in the arterial vessels of the arm It might be argued that the amount of active deposit in the several cubic centimeters of blood that had been withdrawn is greater than might be expected in a strip of artery 2 or 4 cm long To test this point, we examined a few drops of blood of each sample to learn whether the cloud effect could be observed from such small amounts

TABLE 2

Comparison between the circulation times of the same persons obtained by the radium active deposit method and by testing the blood from the brachial artery for the presence of fluorescein

Name	Date	Circulation time		
		Radium method	Arterial puncture	Difference
		seconds	*seconds*	*seconds*
B S	4-9	16	12	4
A. D	4-10	12	10	2
G L	4-10	18	15	3
F D	4-10	19	13	3

Even when only two or three drops of blood were placed on a piece of gauze and held close to the cloud chamber, the ionization effect was unmistakably present The presence of fluorescein was not evident in such small amounts

That radium C can yield so great an effect when present in such small amounts lends further probability to the belief that the onset of the cloud effect is due to the presence of radium active deposit in the larger arteries rather than in the smaller vessels To gain conclusive evidence that the onset of the effect is due to the presence of active deposit in the artery, blood was withdrawn from the arteries of a few individuals The time of arrival of the active deposit in the arterial blood averaged three seconds earlier than the times recorded in the routine measurements in the same individuals (Table 2) The meaning of these

differences is difficult to interpret, since the arm-to-arm circulation times may vary three seconds in the same person Since the circulation times by arterial punctures are in general shorter than the routine determinations, two possibilities may be offered (*a*) the actual time of onset of the ionization effect may not appear until the active deposit enters the smaller arteries, or (*b*) the arterial puncture times may give an earlier result because of the change in the experimental conditions The gradient of pressure within the needle falls from the arterial blood pressure at one end to atmospheric pressure at the other Gradients such as this do not exist normally in the body The flow may be more rapid, therefore, through the needle than it would be with the circulation of the arm undisturbed

The substitution of the normal peripheral resistance by zero pressure at the collecting end of the needle is analogous to the condition existing in arteriovenous aneurysm It is interesting to note that Lewis and Drury (8) found in man that "the quantity of blood leaking from a large limb artery to the corresponding vein in cases of arteriovenous aneurysm may be very considerable, amounting to a fifth or even a half of the quantity thrown out by the left ventricle at each beat" It is plausible, therefore, that the flow from the artery through a needle open to atmospheric pressure may be more rapid than that normally present, and might account for the shorter times observed

VI Variation of dosage

In order to be certain that the results were in no degree influenced by the amounts of active deposit injected, duplicate measurements were made in the same individuals, using greatly varying doses By the time the active deposit injected into the right arm reaches the left, the concentration is diminished due to mixing of the active deposit with the blood It is clear that if the first appearance of radium active deposit were in concentrations below that which could be detected by the ionization chamber, the onset would not be recorded until the aftercoming more concentrated solution of active deposit reached the arteries Such an error would exhibit itself by the recording of shorter velocity times when larger doses were used It is interesting to observe therefore that increase in the number of millicuries injected did not significantly alter the results obtained in a given individual

VII Repeated measurements in the same individuals

Results of any procedure such as the one presented in this paper may reflect variations inherent in the method as well as variations in the phenomenon under investigation The preceding discussion has dealt with the precautions observed in our attempt to reduce to a minimum all variations due to the experimental procedure Under conditions as similar as possible, and observing all the precautions that have been mentioned, we have made successive measurements of the

TABLE 3

Repeated determinations of the circulation time in the same persons by the radium active deposit method

Name	Age	Diagnosis	Date	Circulation time	Date	Circulation time
				seconds		*seconds*
S T	27	Arthritis	8–29	18	9–1	21
I T	53	Auricular fibrillation	8–29	63	9–1	71
F M	43	Auricular fibrillation	8–28	55	9–1	53
L C.	44	Arteriosclerosis	12–2	28	12–4	27
					12–5	26
T W	43	Auricular fibrillation	12–16	57	12–29	47
L B	41	Bronchial asthma	1–5	22	1–5	22
D S	63	Gastro-enteritis (?)	1–5	28	1–5	26
F B	25	Bronchitis	1–6	18	1–6	18
G W	65	Polycythemia	1–11	31	1–12	34
L P	41	Normal	1–11	19	1–12	20
T D	53	Emphysema	3–15	21	4–10	19
L.	52	Tuberculosis (?)	6–18	19	6–21	23
A. D	72	Normal	6–16	24	6–21	23
S S	18	Normal	6–22	18	6–22	23

velocity of blood flow in certain individuals (Table 3) The trustworthiness of the method is verified by the close correspondence of the results As can be seen from the table, observations on certain persons were repeated on the same day while in others they were repeated on successive days According to our experience the minimal time within which the tests can be repeated is three hours Within this period the active deposit of radium decays spontaneously to 3 per cent of its initial value. Direct tests on the urine show that the active deposit appears within a few minutes following its intravenous

TABLE 4

Measurement of the circulation times of normal male individuals and the relation to other cardio-respiratory measurements

Number of measurement	Name	Age	Surface area	Respiration	Pulse	Circulation time	Circulation time per square meter	Vital capacity	Vital capacity per square meter	Arterial pressure		Venous pressure H₂O*	Red blood cell count	Hemoglobin	Millicuries injected
										Systolic	Diastolic				
			square meter			*seconds*	*seconds*	*cc*	*cc*	*mm*	*mm*	*cm*	*millions*	*per cent*	
179	A D	15	1 61	18	102	12	7			130	70	1 5			2 6
62	W F	22	1 82	17	86	15	8	4,600	2,530	108	70	2 1	4 76	104	1 5
26	R B	13	1 40	24	84	11	8	3,000	2,140	112	54	3 0	5 18	105	1 3
172	H G	19	1 88	19	100	15	8	4,800	2,550	128	54	4 5	5 24	102	2 2
186	F N	56	1 70		106	14	8								2 6
64	G H	47	1 93	19	70	18	9			108	62	1 0	4 36	88	1 6
66	G L	50	2 07	19	82	19	9	3,950	1,900	114	72	1 0	3 90	80	1 4
84	B S	48	1 84	15	73	16	9	4,550	2,460	121	66	2 5		95	3 2
88	F E	20	1 63	19	98	15	9	4,150	2,540	128	68	1 4		110	1 1
99	F L	39	1 88	23	81	16	9	3,800	2,050	124	46	4 5	1 05		2 6
101	R I	27	1 67	15	59	15	9	4,300	2,570	104	54	1 5		96	2 2
34	S F	19	1 64	20	71	15	9	3,800	2,310	120	55	1 5	5 10	115	9 1
207	D F	26	2 03	18	78	19	9								3 6
65	E D	35	1 71	17	71	17	10	4,100	2,390	122	66	0 5			3 4
86	F	29	1 67	16	66	16	10	4,250	2,540	80	40	3 4	5 64	105	
102	A	40	1 70	17	60	17	10	3,890	2,290	92	54	4 5	4 82	95	1 7
25	M S	23	1 56	21	72	15	10	4,200	2,690	100	40	3 5	4 13	95	1 1
42	F B	25	1 77	16	57	18	10	3,500	1,920	92	40	1 8	4 50	85	5 1
43	F B	25	1 77	18	56	18	10	3,500	1,920	94	44	1 8	4 50	85	3 9
45	A J	35	1 79	23	86	17	10	4,500	2,510	114	48	4 0	4 40	85	0 8
163	I C	15	1 48	16	61	15	10	3,150	2,250	104	68	−1 5			2 5
170	A H	17	1 57	17	64	16	10	3,200	2,040	118	68	2 5			2 1
173	T C	37	1 74	19	56	17	10	4,750	2,730	118	50	2 5			2 1

177	B S	67	1 60	17	102	16	10	4,250	2,650	136	66	2 8			2 9
181	G L.	48	1 80	18	78	18	10			120	76				2 9
189	C I	22	1 72		86	18	11	4 300	2,520	124	74	3 5			2 5
190	C W	58	1 85		82	20	11	4,550	2,510	135	80	2 5			3 1
201	A D	72	2 28	16	64	24	11			120	64	−3 5			3 1
28	A L	31	1 67	23	72	21	12	3,100	1,860	104	54	3 4	4 86	102	1 6
32	R	18	1 64	17	61	20	12	4 300	2 610	116	80	0 5	5 70	100	1 1
35	A. M	26	1 61	18	62	20	12	3 950	2 450	130	64	1 2	6 23	108	6 7
51	S W	27	1 87	21	82	22	12	5 400	2 880	114	72	2 5	6 20	104	4 5
55	L. P	41	1 78	19	67	20	12	4,900	2,750	110	68	0 0	5 24	108	3 7
67	H T	65	1 56	26	112	19	12	3,100	2 000	130	68	1 0	4 04	85	4 6
72	M G	62	1 65	20	84	20	12	4 000	2,420	170	68	2 5	5 04	95	1 6
83	J T	44	1 53	18	70	18	12	4,000	2,610	134	72	1 4	4 42	96	1 7
47	J G	37	1 67	21	64	21	13	3 400	2,040	102	42	1 0	4 20	90	6 0
77	R. R	40	1 59	16	57	21	13	4,150	2 670	112	54	1 2	5 12	95	2 5
220	S S	18	1 75		70	23	13			110	74				4 6
94	D V	39	1 46	19	65	20	14	3 850	2 630	114	56		5 20	85	2 0
211	A. D	73	2 28		74	23	10								4 3
212	T A.	45	1 65		89	16	10	3,900	2 360	108	58	5 0			4 2
217	S S	18	1 75		78	18	10	3,750	2,140	108	70	2 0			4 2
22	A. L.	45	1 98	20	90	21	11	3,800	1 910	130	76	3 0	4 96	85	1 5
27	R. T	45	1 98	21	80	21	11	3 900	2,000	90	54	3 0	4 96	85	5 5
46	G B	25	1 58	22	82	18	11	3,000	1,890	104	40	2 0	4 60	85	4 0
54	L. P	41	1 78	19	77	19	11	4,900	2 750	108	66	3 0	4 96	94	5 2
81	T E.	43	1 81	19	64	19	11	4,350	2,400	130	68	1 2	3 96	75	1 4
92	K H.	36	1 67	17	70	19	11	4 850	2,900	94	54	3 0	4 20	68	2 5
93	A C	60	1 73	19	76	19	11	3 850	2,230	112	68	1 0	4 04	84	1 7
103	A. J	51	2 00	12	82	22	11			152	100	2 5		70	1 2
166	A. B	25	1 71	16	61	18	11	4,550	2,660	120	84	3 5		105	2 5
184	W M	69	1 69		92	18	11								2 9

* To correspond to the level of the right auricle, 5 0 cm. should be added to these measurements.

injection Less than the theoretical 3 per cent is present within the body at the end of three hours

VIII Single measurements in normal individuals

The fundamental functions of a system as complex as the circulation are many Isolated measurements of a single aspect are difficult to interpret To gain as much insight as possible into the significance of velocity measurements, we therefore observed as many related phenomena as possible (table 4) The age, the height, and the weight were recorded The blood pressure, the respiratory rate, the mouth temperature, and the ventricular rate were noted just before the velocity of blood flow was determined The ventricular rate was counted again immediately after each measurement and never varied more than ten beats from its previous rate The venous pressure was measured immediately before the active deposit of radium was injected The vital capacity of the lungs was ascertained and the blood was examined on the day the velocity of blood flow determination was made The hemoglobin was measured by the Tallquist method The results of our observations are tabulated below

DISCUSSION

For the purpose of establishing a critique of the method it was necessary to measure the velocity of blood flow in patients who exhibited various lesions of the circulatory system The following discussion refers, however, solely to the data derived from the study of normal male individuals (table 4) All the subjects were males, convalescent from diseases neither metabolic nor cardio-respiratory, nor haemic in origin The related data recorded in the tables, the careful histories and physical examinations at the time of the test establish the normality of these individuals Most of them were about to be discharged from the surgical services They may be regarded as satisfactory controls These patients might not be considered as strictly normal because of their stay in the hospital, nevertheless we believe they serve as a more accurate basis of comparison to patients similarly hospitalized, who exhibited pathological lesions of the circulatory system Moreover, hospitalization probably exerts no significant effect on the velocity of blood flow since some

individuals who were not hospitalized showed times essentially similar to the "normal" hospitalized men

Relation of age to the velocity of blood flow

The basal metabolic rate tends to become lower with advancing age and it is therefore of interest to learn whether the velocity of blood flow undergoes an analogous change There is apparently in normal individuals no critical age beyond which the velocity of blood flow becomes slower (Table 5) The velocity of blood flow in a normal adult individual, therefore reflects the actual condition of the circulation, independent of age The circulation times of children between

TABLE 5

The relation of the average circulation times of normal male persons to the age, the surface area and to the vital capacity

Age	Number of cases	Circulation time	Variations	Circulation time per square meter	Variations	Vital capacity	Vital capacity per square meter
		seconds	*seconds*	*seconds*	*seconds*	*cc.*	*cc.*
15–29	22	17	12–23	10	7–13	4 000	2 390
30–39	8	19	16–21	11	8–14	4 170	2,430
40–49	12	19	16–21	11	9–13	4 070	2 370
50–75	12	19	14–24	11	8–14	3 720	2 160

the ages of twelve and fifteen, obtained in a few determinations appear to be shorter both in absolute values and in values reduced to square meter of body surface

Relation of blood pressure to the velocity of blood flow

Other factors remaining constant, the velocity of blood flow between any two points is proportional to the difference in pressure between these two points, and is inversely proportional to the resistance Were all the factors of the circulation to remain constant, we might expect that when the venous pressure is zero, the higher the mean arterial pressure, the greater would be the velocity of blood flow It is of interest to learn, therefore, whether an increase in blood pressure tends to be associated with an increase in the velocity of blood flow The systolic blood pressures in these individuals ranged from 80 to

136 mm , and the diastolic from 41 to 66 In two persons, however, the measurements were 170 and 152 mm systolic, and 68 and 100 mm diastolic, respectively, although in them no disease of the circulation was discovered either on physical examination or by the usual tests The increase in blood pressure may have been due to excitement at the time of the measurement of velocity of blood flow Examination of our data reveals no evident relation between physiological variation in blood pressure and physiological variation in circulation time In normal individuals increased blood pressure is probably associated, therefore, with proportionate increase in peripheral resistance Further description of the dynamics of the arterial blood pressure and its relationship to the velocity of blood flow will be reserved for a later communication in which the results in subjects with hypertension will be discussed

Relation of the ventricular rate to the velocity of blood flow

Although the ventricular rates of these subjects varied from 56 to 112, there was no corresponding alteration in the velocity of blood flow This is not surprising inasmuch as the velocity of blood flow is more closely related to the minute volume output, which in turn is a product of the stroke volume times the ventricular rate It is interesting to note that the minute volume output does not necessarily bear a direct relationship to the ventricular rate E K Marshall (9) using the direct Fick method in trained unanesthetized dogs, found in four dogs that the ventricular rate may vary from 50 to 250 without change in the minute volume output In a pregnant dog there was, however, an increased output with an increase in the pulse rate

In twenty-one[4] normal individuals of various ages the ventricular rate at the time of the test was higher than eighty, the average being ninety The average circulation time of these individuals was seventeen seconds, the average circulation time per square meter of body surface was ten seconds In five[5] normal individuals in whom the ventricular rate averaged one hundred and four, the average circulation time was fifteen seconds and the average circulation time per

[4] These are patients number 22, 26, 45, 46, 51, 62, 66, 67, 72, 88, 99, 103, 177, 179, 184, 186, 189, 190, 195, 212, 127, table 4

[5] These are patients number 67, 177, 179, 186, 172, table 4

square meter of body surface was nine seconds The findings indicate, therefore that in normal resting individuals with a rather considerable increase in ventricular rate there tends to be only a slight increase in the velocity of blood flow

On the other hand in five normal[6] persons whose ventricular rate was less than sixty at the time of the test (average fifty seven), the average circulation time was eighteen seconds, or ten seconds per square meter The finding therefore indicates that in these individuals the slow ventricular rate was not associated with an appreciable slowing of the blood flow The relation of abnormal ventricular rates and rhythms to the velocity of blood flow will be discussed in a subsequent communication

Relation of surface area to the velocity of blood flow

It has long been known that both the heat production in man and the vital capacity bear a definite relationship to the surface area The average circulation time of individuals between the ages of fifteen and twenty-nine was seventeen seconds, and when reduced to surface area was ten seconds In the persons between the ages of thirty and seventy five the average circulation time was found to be nineteen seconds, or, in terms of surface area, eleven seconds per square meter The deviation from the mean remained proportionately about the same whether the actual circulation time was taken or whether the time was referred to the surface area

Significance of the variations in velocity of blood flow in normal individuals

Successive velocity measurements in a given normal individual have not varied by more than three seconds except in two instances, the extreme range from one individual to another has amounted to ten seconds The cause of this variation, can, in all probability not be assigned to a single factor Vasomotor instability, peripheral resistance, character of the vessel walls, length of the path traversed, cross-sectional area of the vessels, force of cardiac systole, minute volume output—all these play important rôles in controlling the velocity of

[6] These were patients number 42, 43, 77 101, 173, tables 4

blood flow It is manifestly impossible to venture an opinion on the basis of the now available facts as to the relative importance of these conditions in causing the variation which we have observed

CONCLUSIONS

1 The chief precautions observed in estimating the velocity of blood flow by the radium active deposit method are described

2 Direct and indirect evidence is presented that the ionization effect is due to the radiation which emerges from the arterial blood of the arm

3 Considerable variations of the dose of the active deposit of radium do not influence the results obtained

4 Repeated measurements in eleven individuals with regular rhythm agreed within an average of two seconds The variation never was more than three seconds except in two individuals in whom it amounted to four seconds and five seconds, respectively

5 Measurements can be repeated as early as three hours

6 The circulation times of fifty-three normal resting male individuals are presented

7 The arm to arm circulation time in normal resting individuals may vary between fourteen and twenty-four seconds when the active deposit is injected into the cubital vein of one arm and the onset of radiation from the arterial vessels of the other arm is detected

8 The arm to arm circulation time does not become more prolonged with advancing age as measured by the method described There is no critical age beyond which the velocity of blood flow tends to diminish

9 The average arm to arm circulation time in fifty-three normal persons between the ages of fifteen and seventy-five was eighteen seconds

10 The average arm to arm circulation time when reduced to square meter of body surface was ten seconds in individuals between the ages of fifteen and twenty-nine, and eleven seconds between the ages of thirty and seventy-five

11 A few measurements in children indicate that the velocity of the blood flow is somewhat rapid in childhood

12 With a conspicuous increase in the pulse rate there is a slight but definite tendency toward an increased velocity of blood flow

13 A relatively low ventricular rate does not seem to lower the velocity of blood flow below that exhibited by individuals with higher ventricular rates

14 Normal variations in the blood pressure bear no relation to the normal variations in the velocity of blood flow

We wish to express our appreciation to Dr Francis W Peabody for his constant advice and encouragement

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INORGANIC SULPHATES IN HUMAN BLOOD

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INTRODUCTION

In recent years, many of the electrolytes of the blood have been intensively studied under normal and pathological conditions in human beings The inorganic sulphate ion has not participated in this general interest, as has been pointed out by Denis (1), because of the minute amounts normally present and because of its apparent lack of importance from a physiological standpoint

Denis, in 1921, reported a large number of SO_4 determinations, made nephelometrically, on human blood in normal individuals and in various diseases In view of the fact that this is the only comprehensive study of this subject in addition to those of White (2) and Kahn (3), it seems justifiable to report a similar series of observations made some years ago by a *gravimetric* method even though the results merely confirm those of Denis

METHOD

One drop of caprylic alcohol and 10 cc of serum are placed in a 50 cc volumetric flask To this are added 10 cc of water and 30 cc. of saturated aqueous picric acid solution After thorough mixing, the contents are *rapidly* centrifuged (to avoid evaporation) and the supernatant fluid is filtered A 30 cc. aliquot is placed in a 50 cc. beaker and 5 cc. of one per cent $BaCl_2$ solution are slowly added The precipitation is allowed to go on for at least 6 hours and then the solution is filtered through a 7 cm ash free filter paper (sometimes two to four filtrations are necessary) and the precipitate is washed 5 times with 4 cc. of water acidulated with HCl The filter is ignited slowly in a weighed platinum crucible with the lid only slightly open until charring has occurred Later, the lid is kept about half open to prevent excessive reduction of $BaSO_4$ Care must be taken not to allow the filter to burst into flame. Ignition should take about 25 minutes The crucible should be weighed as soon as it is cool A certain amount of reduction of

TABLE 1

Addition and recovery of SO_4 from serum

SO_4 added	SO_4 recovered	Calculated as SO_4 per 100 cc. serum	
		Found	Theoretical
mgm	*mgm*	*mgm per 100 cc*	*mgm per 100 cc.*
2 00	1 92	26 0	26 8
2 00	1 85	21 2	22 7
2 00	1 89	24 7*	25 8
2 00	1 89	25 6*	25 8
2 00	2 05	27 4†	26 9
2 00	2 19	28 8†	26 9
1 00	0 89	15 1	16 1
1 00	1 30	17 8	14 8

N B Determinations marked (*) and (†) are duplicates

TABLE 2

Normals

Number	$BaSO_4$ weighed	Expressed as SO_4 in serum		Urea N	Non protein N
	mgm	*mgm per 100 cc*	*mEq per L*	*mgm per 100 cc*	*mgm per 100 cc*
Lo	0 4	2 7	0 6	13 3	28 3
Lo	0 5	3 4	0 7	12 2	35 4
Zi	0 6	4 1	0 9		
Re	0 7	4 8	1 0		
Se	0 3	2 1	0 4		
We	0 5	3 4	0 7		
Be	0 5	3 4	0 7		
Ru	0 5	3 4	0 7		
La	0 6	4 1	0 9	17 3	
So	0 6	4 1	0 9		
Ti	0 2*	2 4	0 5		
Ho	0 4*	3 4	0 7	12 5	24 0
At	0 4	2 7	0 6		32 9
Average normal		3 4	0 7		
Highest normal		4 8	1 0		
Lowest normal.		2 1	0 4		

* Seven cubic centimeters of serum and a 35 cc aliquot were used instead of the customary 10 cc. of serum and a 30 cc. aliquot.

$BaSO_4$ appears to take place but the errors resulting therefrom are not significant While the amounts weighed are very small and while there are several sources of possible error, the results obtained with the method have been fairly constant

TABLE 3

Cardiac and renal disease

Name	Diagnosis	BaSO₄	Expressed as SO₄ in serum		Urea N	Non-protein N
		mgm	*mgm per 100 cc.*	*mEq per L.*	*mgm per 100 cc*	*mgm per 100 cc*
Gray	Toxemia of pregnancy	0 8	5 5	1 1		
Gray	Toxemia of pregnancy	0 5*	4 2	0 9	14 7	30 0
Di Leonardo	Mitral disease	0 9	6 2	1 3		
Schuhmacher	Acute nephritis	1 2*	10 0	2 1	48 3	75 0
Garntyuk (duplicate)	Chronic nephritis	1 4	9 6	2 0		68 0
		1 3	8 8	1 8		
Garntyuk	Chronic nephritis	1 3	8 9	1 9		49 2
Gordon	Hypertension	0 6	4 1	0 9	9 3	
Wilkins	Hypertension	0 9*	7 5	1 6	18 7	37 8
Snufsky	Uremia	7 5	51 4	10 7	158 0	214 0
Snufsky	Uremia	5 7	39 0	8 1	138 0	200 0
Mason	Hypertension	0 8	5 5	1 1	9 0	22 0
Andrews	Chronic nephritis	0 9	6 2	1 3	15 4	33 8
Putney	Cardiac decompensation	1 5	10 3†	2 2		38 0
Williamson	Hypertension	1 0	6 9	1 4		55 0
Galloway	Hypertension	0 7*	5 9	1 2		40 0
Brown	Hypertension	0 9	6 2	1 3		46 1
Geo Smith	Hypertension	1 0	6 9	1 4	19 9	36 5
Sava	Chronic nephritis	5 4	37 0	7 7		160 0
Taylor	Chronic nephritis	2 1	14 4	3 0		111 0

* Seven cubic centimeters of serum and a 35 cc. aliquot were used instead of the customary 10 cc. of serum and a 30 cc. aliquot.

† Following Mg SO_4 administration

TABLE 4

Miscellaneous cases

Name	Diagnosis	BaSO₄ weighed	Expressed as SO₄ in serum		Urea N	Non-protein N
		mgm.	*mgm. per 100 cc.*	*mEq per L*	*mgm per 100 cc.*	*mgm. per 100 cc.*
1	Rheumatic fever	0 4	2 7	0 6		
2	CNS lues	1 0	6 8	1 4		
	Acute glaucoma	0 7	4 8	1 0		
3	Pneumonia	0 9*	7 5	1 6	14 3	28 7
4	Pernicious anemia	0 7	4 8	1 0		
5	Portal cirrhosis	0 5	3 4	0 7		41 6
6	Diabetes mellitus	0 8	5 5	1 1		

* Seven cubic centimeters of serum and a 35 cc. aliquot were used instead of the customary 10 cc. of serum and a 30 cc. aliquot.

RESULTS

From table 1 it may be seen that addition and recovery determinations of sulphate added to serum are quite satisfactory Table 2 shows that the sulphate content of normal serum is approximately the same as that obtained by Denis Table 3 shows that the concentration of SO_4 in the blood of patients suffering from cardiac and renal disorders is at times markedly increased and that it nearly parallels the retention of nitrogen Table 4 shows that there is little deviation from the normal SO_4 values in certain other pathological conditions

CONCLUSIONS

1 The normal SO_4 content of serum varies between 0 40 and 1 00 milli-equivalent per liter when determined by the *gravimetric* method described above and the results are in close agreement with the findings of Denis

2 In nephritis with nitrogen retention the SO_4 ion is retained in the blood and roughly parallels the non-protein nitrogen as Denis has shown The concentration of SO_4 in serum may reach 10 milli-equivalents per liter

3 Inorganic SO_4 plays a relatively important rôle in the partition of the acid radicals in the blood in nitrogen retention nephritis

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PREFERENTIAL UTILIZATION OF CARBOHYDRATE IN DIABETES[1] [2]

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INTRODUCTION

Surveying the history of the treatment of diabetes in man, one finds that persistent attempts have been made from time to time, to feed other carbohydrates than glucose, in the hope that they would be utilized when the power to utilize glucose itself had been seriously interfered with (or in the hope that a greater amount of the substance might be utilized than if glucose were used) So far as we know glucose is the only form in which carbohydrate is ultimately used in the tissues of the normal animal, and if it could be shown that other carbohydrates are better used by the diabetic organism, which we suggest might be called a preferential utilization of the carbohydrate—a very important principle in the treatment of the diabetic would be established, both from the standpoint of the provision of energy directly through the caloric value of the carbohydrate and because of the additional safeguard which would be provided against ketogenesis, (assuming, of course, that the carbohydrate has antiketogenic properties)

The evidence in favor of preferential utilization of carbohydrate has, at best, been rather meagre and rests principally on clinical observations on diabetes in man Sometimes the observations have been imperfectly controlled and the results would not today be admitted in evidence, but even when every precaution has been taken

[1] Read at the 18th Meeting of the American Society for Clinical Investigation, May 3, 1926 Abstract J Clin Invest 1926, ii 608

[2] The dihydroxyacetone used in these investigations was purchased by a grant from the John D Rockefeller Jr fund of the Diabetic Clinic, Toronto General Hospital

the evidence, interpreted in the light of our present views of diabetes, is not nearly so impressive as it formerly appeared to be. In many cases also the period during which the substance in question was given has not been sufficiently long to allow of any accurate conclusions being drawn, especially because the possibilities of storage of the carbohydrate in the form of glycogen, or blood and tissue sugar, or as fat have been inadequately considered. Less frequently the question of absorption from the gastro-intestinal tract has been a doubtful factor in the interpretation of results. While in the milder cases of diabetes there may have appeared some ground for believing that certain of these substances could be preferentially metabolized it is significant that the earlier conclusions have failed to pass the test of time.

Under certain circumstances it has been shown that more glycogen may be stored, temporarily at least, in the liver of depancreatized animals when carbohydrates other than glucose—levulose for example—are being fed. In all probability a knowledge of this storage has been misleading in the interpretation of the observations in man, for it does not necessarily follow that glycogen storage in the liver bears any relation to the actual burning of carbohydrate in the body (it is without any real significance in the question of preferential utilization of carbohydrate). Ignorance of the production and properties of insulin have also stood in the way of a correct interpretation of the results, especially the facts that the internal secretion of this hormone can be inhibited or stimulated by various means, such as food administration or perhaps exercise, and that it behaves like an enzyme or catalyst in relation to the amount of carbohydrate available in the body for it to act on.

These facts, as well as the uncertainties of the daily production of insulin by the pancreas of diabetic patients, makes it exceedingly difficult to evaluate the results of carbohydrate utilization. We have therefore, attempted in the present investigation to gain more precise knowledge by using depancreatized dogs in which many of these sources of error can be controlled. For those who insist on regarding the diabetes of the depancreatized animal as essentially different from the human disease, the transfer of the problem to the laboratory animal may seem to constitute a fundamental drawback to the applicability

of the results to man Since there remains, however, no feature of the human disease which by appropriate treatment cannot be precisely duplicated on the depancreatized animal we do not consider the objection as valid

EXPERIMENTAL

Young, adult, female dogs weighing from 7 to 10 kgm were used The pancreas was entirely removed and the perineum slit under ether anesthesia, after which the animals were placed in metabolism cages and fed twice daily with diet consisting of chopped lean meat (200 grams), raw pancreas (50 grams) and glucose (20 grams) Sufficient insulin was also injected to maintain the animals in nitrogenous equilibrium without however, entirely suppressing glycosuria. To accomplish this it was found best to inject 10 U insulin into the lumbosacral region daily, at the time of the animals' feeding They took their food with relish and consumed all of it immediately By following this routine a known and constant amount of insulin was acting during the period of food absorption, and the animals soon got into excellent bodily condition and recovered and maintained their normal weights They were kept in this way for some time so that by becoming accustomed to living in the metabolism cage the element of muscular exercise might remain constant. The animals were catheterized and the bladder irrigated at the same hour each morning, just prior to feeding, and the urine thus obtained was added to that passed during the 24 hours, along with the cage washings Having observed the daily carbohydrate balance on the above diet for some time, an equal weight of levulose inulin, dihydroxyacetone or glycerol was substituted for the glucose during a four day period all the other factors remaining the same This test period was then followed by another control period in which glucose was replaced in the diet of the animal It may here be stated in parenthesis that we have found that it takes about six hours for complete recovery in the urine of 20 grams of glucose given by mouth, provided water is meanwhile freely allowed the animals

The urines were analyzed for total sugar by Benedict's copper reduction method, and for fructose, inulin and dihydroxyacetone by polarimetry, fermentation, and by the use of specific tests when necessary Total nitrogen was determined by the Kjeldahl method Acetone bodies and inorganic phosphates were determined by Van Slyke's method (1) and by Brigg's method (2) respectively Since acetone bodies were absent or at most were present in mere traces, the figures have been omitted from the tables In the case of inulin the feces were examined for this substance the periods being marked off by charcoal administration After the ingestion of dihydroxyacetone or of fructose or inulin the blood was examined for the presence of these substance by the methods which have recently been described by one of us (3 4) The test substances used were high grade products and, if necessary they were re-purified in the laboratory The weight of carbohydrate administered was the weight of the anhydrous substance

RESULTS

These are shown in the tables, in which it has been considered unnecessary to include the daily body weights of the animals, since these did vary not for each animal by more than about 120 grams during the course of many of the observations The nitrogen excretion can be seen to have been practically constant from day to day, since it was approximately equal to the nitrogen intake in the food It

TABLE 1

Dog F Levulose

Date	Carbohydrate fed	Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
	grams	*grams*	*grams*	*grams*
February 4	Glucose 40	14 7	23 1	
February 5	Glucose 40	12 5	23 9	21 4
February 6	Glucose 40	12 4	17 8	
February 7	Glucose 40	21 8	21 8	
February 8	Levulose 40	13 6	27 7	
February 9	Levulose 40	13 8	26 5	25 1
February 10	Levulose 40	13 8	25 9	
February 11	Levulose 40	14 1	22 5	
February 12	Glucose 40	14 5	29 0	
February 14*	Glucose 40	12 9	13 2	20 8
February 15	Glucose 40	14 0	20 2	
February 27	Glucose 40	13 9	9 8	
February 28	Glucose 40	14 9	18 0	20 9
March 1	Glucose 40	13 3	26 8	
March 2	Glucose 40	13 1	29 2	
March 3	Levulose 40	13 0	19 6	
March 4	Levulose 40	12 6	17 1	17 6
March 5	Levulose 40	12 3	13 3	
March 6	Levulose 40	13 4	20 4	
March 7	Glucose 40	13 1	27 7	
March 8	Glucose 40	13 3	30 2	27 1
March 9	Glucose 40	12 9	23 5	

* February 13, specimen lost

seems improbable that the animals were either destroying their own tissue protein or were laying on protein or fat in any significant quantity The daily excretion of carbohydrates was not so constant, but the variability shown is not greater than would be expected in

TABLE 2

Dog III Levulose

Date	Carbohydrate fed	Excretion		Sugar excreted average
		Nitrogen	Sugar	
	grams	*grams*	*grams*	*grams*
February 4	Glucose 40	14 0	34 5	29 2
February 5	Glucose 40	14 2	30 5	
February 6	Glucose 40	13 6	25 7	
February 7	Glucose 40	13 4	26 1	
February 8	Levulose 40	15 0	29 5	24 8
February 9	Levulose 40	13 1	18 2	
February 10	Levulose 40	12 5	23 5	
February 11	Glucose 40	14 0	28 0	31 4
February 12	Glucose 40	14 8	39 0	
February 13	Glucose 40	13 3	31 8	
February 14	Glucose 40	12 0	31 2	
February 15	Glucose 40	12 7	25 5	
February 20	Glucose 40	13 3	27 8	24 9
February 21	Glucose 40	13 3	31 6	
February 22	Glucose 40	12 5	15 2	
February 23	Levulose 40	13 7	17 4	18 2
February 24	Levulose 40	13 9	22 2	
February 25	Levulose 40	12 7	18 1	
February 26	Levulose 40	13 6	14 9	
February 27	Glucose 40	13 7	18 1	20 4
February 28	Glucose 40	13 5	22 5	
March 1	Glucose 40	13 6	21 8	
March 2	Glucose 40	12 5	19 4	

work of this character although it is greater during the test period than during the control periods It may also be remarked that there was no significant variation in the excretion of inorganic phosphorus, which, however, was relatively high, no doubt because of the larger

quantities of meat and pancreas contained in the food It is possible that in view of this high excretion, any changes in relation to carbohydrate metabolism might be masked by the amount of phosphorus being excreted

Levulose The observations were made on three dogs, the results on dog F being shown in table 1, those on dog 3 in table 2 and those on dog 1 in table 3 In the interval between the recorded observations the dogs in tables 1 and 2 were kept on the routine diet except that glycerine was substituted for glucose The results of table 1 show that

TABLE 3

Dog I Levulose

Date	Carbohydrate fed	Excretion		Sugar excreted average
		Nitrogen	Sugar	
	grams	*grams*	*grams*	*grams*
February 4	Glucose 40	15 1	19 8	16 9
February 5	Glucose 40	14 4	14 14	
February 6	Glucose 40	14 4	16 9	
February 7	Glucose 40	13 7	16 7	
February 8	Levulose 40	13 9	14 9	13
February 9	Levulose 40	13 9	9 1	
February 10	Levulose 40	14 1	15 8	
February 11	Levulose 40	13 7	12 0	
February 12	Glucose 40	14 2	13 3	10 8
February 14*	Glucose 40	14 1	6 05	
February 15	Glucose 40	14 3	13 0	

* February 13, specimen lost.

the substitution of levulose for glucose caused an increase in the daily excretion of glucose in the first series of observations, but a decrease of about the same magnitude during the second The excretion of nitrogen also declined somewhat along with that of glucose in the second period The grand average for the daily excretion of glucose on all the glucose days of both periods of observation is 22 5 grams as compared with 21 3 for the fructose days Levulose was detected in small concentration in the urine of these animals qualitatively by Seliwanoff's and Borchardt's reactions but its amount as determined

by the difference in the copper reduction and polarimetric estimations of sugar was extremely small and would make no significant change in the calculations Levulose was detected in the blood of the animal

TABLE 4

Dog I Inulin

Date	Carbohydrate fed	Excretion		Sugar excreted average
		Nitrogen	Sugar	
	grams	*grams*	*grams*	*grams*
February 20	Glucose 40	13 5	21 1	
February 21	Glucose 40	12 2	12 2	16 8
February 22	Glucose 40	13 7	17 0	
February 23	Inulin 40	13 3	12 9	
February 24	Inulin 40	13 3	9 9	11 4*
February 25	Inulin 40	13 3	14 6	
February 26	Inulin 40	21 8	9 1	
February 27	Glucose 40	14 0	14 5	
February 28	Glucose 40	14 3	29 0	23 7
March 1	Glucose 40	13 9	24 0	
March 2	Glucose 40	13 2	27 5	
Dog F Inulin				
February 20	Glucose 40	13 1	15 0	
February 21	Glucose 40	13 2	17 4	14 2
February 22	Glucose 40	12 5	10 3	
February 23	Inulin 40	12 7	11 1	
February 24	Inulin 40	12 9	10 1	9 2†
February 25	Inulin 40	12 6	12 1	
February 26	Inulin 40	12 5	3 2	
February 27	Glucose 40	13 9	9 75	
February 28	Glucose 40	14 9	18 0	20 9
March 1	Glucose 40	13 3	26 8	
March 2	Glucose 40	13 1	29 2	

* 76 3 grams inulin recovered from feces = 19 1 grams per day

† 61 grams inulin recovered from feces = 15 2 grams per day Levulose found in blood

during the period of levulose feeding by the method recently described (4), indicating that the carbohydrate was being absorbed as such and converted to glucose by the organism

The results on dog 3 (table 2) show that the carbohydrate excretion was approximately equal or slightly less on the days when levulose was administered than when glucose was given, but the differences are hardly significant The results on the third dog (table 3) though, unfortunately, incomplete also show slight decreases in both nitrogen and glucose during the levulose periods

Inulin Table 4 shows the results obtained on two dogs (F and I of tables 1 and 3) when inulin was substituted for glucose in the diet The inulin used was a high grade commercial product which we

TABLE 5

Dog F Dihydroxyacetone

Date	Carbohydrate fed		Excretion		Sugar excreted average
			Nitrogen	Sugar	
		grams	*grams*	*grams*	*grams*
January 28	Glucose	40	13 4	27 8	18 1
January 29	Glucose	40	13 3	19 5	
January 30	Glucose	40	13 9	16 7	
January 31	Dihydroxy acetone	40	13 8	18 3	19 6
February 1	Dihydroxy acetone	40	13 6	22 7	
February 2	Dihydroxy acetone	40	13 6	19 3	
February 3	Dihydroxy acetone	40	13 4	18 2	
February 4	Glucose	40	14 7	23 1	21 4
February 5	Glucose	40	12 5	23 9	
February 6	Glucose	40	12 4	17 8	
February 7			14 4	21 8	

reprecipitated by alcohol It contained no glucose or sucrose and little, if any, levulose After drying at 110°C it analyzed over 99 5 per cent inulin It can be seen that decidedly less glucose was excreted on the days during which this polysaccharide was substituted for glucose This is adequately accounted for by an imperfect absorption, for the decreased excretion coincides with a failure to absorb an average of 15 to 20 grams of inulin per day, which was recovered from the feces of the animal The fact that levulose was detected in the blood is evidence that the unrecovered inulin was not wholly destroyed by bacterial enzymes and that part of the inulin was

absorbed This no doubt furnished the source for the urinary glucose since the unchanged or even slightly decreased nitrogen output, as compared with the control days, is evidence against increased protein

TABLE 6

Dog I Dihydroxyacetone

Date	Carbohydrate fed	Excretion		Sugar excreted average
		Nitrogen	Sugar	
	grams	*grams*	*grams*	*grams*
January 27	Glucose 40	13 7	17 1	
January 28	Glucose 40	14 5	9 7	14 5
January 29	Glucose 40	13 3	13 0	
January 30	Glucose 40	13 9	18 2	
January 31	Dihydroxy acetone 40	15 0	11 7	
February 1	Dihydroxy acetone 40	13 4	15 2	11 9
February 2	Dihydroxy acetone 40	13 95	9 7	
February 3	Dihydroxy acetone 40	13 5	11 0	
February 4	Glucose 40	15 1	19 8	
February 5	Glucose 40	14 4	14 14	16 9
February 6	Glucose 40	14 4	16 9	
February 7	Glucose 40	13 7	16 7	
Same dog	*Same routine except 20 grams carbohydrate and 6 units insulin*			
December 10	Glucose 20	13 56	6 95	
December 11	Glucose 20	13 42	8 05	6 7
December 12	Glucose 20	13 02	6 72	
December 13	Glucose 20	11 30	5 00	
December 14	Dihydroxy acetone 20	12 7	1 4	
December 15	Dihydroxy acetone 20	12 4	6 0	3 6
December 16	Dihydroxy acetone 20	13 1	4 62	
December 17	Dihydroxy acetone 20	13 3	5 49	
December 18	Glucose 20	12 98	5 0	
December 19	Glucose 20	13 28	4 65	4 2
December 20	Glucose 20	13 02	2 98	

destruction being responsible for the sugar It is worthy of note that the excretion of sugar in the control period following the administration of inulin is in each case greater than in the preliminary control

period but the explanation for this occurrence is not apparent It is not accompanied by any significant change in nitrogen excretion Allowing for the fact that forty grams of inulin is equivalent to 44

TABLE 7

Dog III Dihydroxyacetone

Date	Carbohydrate fed		Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
		grams	*grams*	*grams*	*grams*
January 27	Glucose	40	13 9	26 25	
January 28	Glucose	40	14 1	25 00	25 8
January 29	Glucose	40	12 4	18 10	
January 30	Glucose	40	14 1	34 00	
January 31	Dihydroxy acetone	40	14 0	17 8	
February 1	Dihydroxy acetone	40	12 2	13 3	20 2
February 2	Sample lost				
February 3	Dihydroxy acetone	40	13 5	29 5	
February 4	Glucose	40	14 0	34 5	
February 5	Glucose	40	14 2	30 5	29 2
February 6	Glucose	40	13 6	25 7	
February 7	Glucose	40	13 4	26 1	

Dog III Known diet 2 days

Date	Carbohydrate fed		Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
December 10	Glucose	20	11 57	14 7	
December 11	Glucose	20	11 41	12 5	12 9
December 12	Glucose	20	12 08	13 5	
December 13	Glucose	20	11 6	12 0	
December 14	Dihydroxy acetone	20	12 2	8 5	
December 15	Dihydroxy acetone	20	12 5	19 0	14 1
December 16	Dihydroxy acetone	20	12 2	7 0	
December 17	Dihydroxy acetone	20	12 4	21 8	
December 18	Glucose	20	13 46	22 4	
December 19	Specimen lost				20 2
December 20	Glucose	20	12 56	18 0	

grams of levulose, the sum of the glucose excreted in the urine plus the inulin recovered from the feces is practically the same as the glucose excretion on the control days, so that the results are interpreted as

showing that inulin is metabolized by the partially diabetic organism to the same extent as glucose (From this evidence as well as from the known chemical instability of inulin it would seem inadvisable to regard it as an indifferent substance wholly unmetabolized by the diabetic On the other hand there is no evidence that it is metabolized by the diabetic organism with any greater facility than is glucose)

Dihydroxyacetone The results of the experiments when dihydroxyacetone was used as the test substance are shown in tables 5 to 7 the same animals being used as in tables 1–3 The results in table 5 show no change in the glucose excretion during the period in which dihydroxyacetone was substituted for glucose. In arriving at this conclusion we have omitted from the averages of the preliminary control period the excessive glucose excretion of the first day, which no doubt was due to the fact that the animal had only been placed on the weighed diet on the previous day

In tables 6 and 7 the results sometimes show a slight decrease in glucose excretion in the periods during which dihydroxyacetone was substituted, but this cannot be taken as evidence of a preferential utilization of this substance over glucose It is probably to be accounted for by some of the dihydroxyacetone which escapes conversion into glucose during its passage through the liver being absorbed and stored in the tissues in which normally none of this substance is present As the tissues become thus loaded with unconverted dihydroxyacetone a part will no doubt gradually return to the blood and increase the glucose production, and it may be on account of this that a tendency can be seen in certain of the observation for the glycosuria to become greater on the last day or so of dihydroxyacetone administration, as well as during the first few days of the subsequent glucose control period

A somewhat different type of experiment is recorded in table 8 A dog, recently depancreatized and thereafter on a variable diet containing meat, raw pancreas and sugar with insulin, was given 200 grams meat, 50 grams pancreas and 40 grams sucrose with 10 units of insulin twice daily As the glucose excretion kept falling in all probability our three preliminary control days do not represent an equilibrium between utilization and excretion of carbohydrate For four days the animal was then given 20 grams dihydroxyacetone *in addition* to the sucrose

in the diet, in two portions of 10 grams each per day This period is followed by a second control period of four days The average of the seven control days' excretion of carbohydrate is 13 2 grams Averaging the four days after control periods gives 10 4 grams of glucose The average glucose excretion in the test period is 27 4 grams The excess excretion of sugar during this period is 14 2 to 17 grams The difference between the amount of extra carbohydrate fed and the

TABLE 8

Dog I Dihydroxyacetone

Date	Carbohydrate fed		Excretion		Sugar excreted average
			Nitrogen	Sugar	
		grams	*grams*	*grams*	*grams*
November 20	Sucrose	40	13 6	21 7	13 2
November 21	Sucrose	40	13 1	16 2	
November 22	Sucrose	40	12 7	12 6	
November 23	Sucrose + Dioxy	40 20	13 0	27 5	27 4
November 24	Sucrose + Dioxy	40 20	13 5	30 4	
November 25	Sucrose + Dioxy	40 20	13 6	25 6	
November 26	Sucrose + Dioxy	40 20	13 5	26 1	
November 27	Sucrose	40	13 3	7 60	10 4
November 28	Sucrose	40	13 4	7 05	
November 29	Sucrose	40	14 6	13 40	
November 30	Sucrose	40	12 2	13 70	

increased excretion is not, however, evidence of preferential utilization of the dihydroxyacetone Should dihydroxyacetone be the intermediate stage between glucose and CO_2 and the water, as has been thought, it should have been wholly metabolized without insulin As has been shown elsewhere (5) when insulin is absent no dihydroxyacetone is burned by the depancreatized animal The small discrepancy between recovered extra glucose and dihydroxyacetone

TABLE 9

Dog F Glycerine

Date	Carbohydrate fed	Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
	grams	*grams*	*grams*	*grams*
February 12	Glucose 40	14 5	29 0	
February 13*	Glucose 40			20 8
February 14	Glucose 40	12 9	13 2	
February 15	Glucose 40	14 0	20 2	
February 16	Glycerine 40	14 1	22 1	
February 17	Glycerine 40	14 3	24 5	24 2
February 18	Glycerine 40	13 7	23 9	
February 19	Glycerine 40	13 7	26 4	
February 20	Glucose 40	13 1	15 0	
February 21	Glucose 40	13 2	17 4	14 2
February 22	Glucose 40	12 5	10 3	

Dog I Glycerine

Date	Carbohydrate fed	Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
February 12	Glucose 40	14 2	13 3	
February 14	Glucose 40	14 1	6 1	10 8
February 15	Glucose 40	14 3	13 0	
February 16	Glycerine 40	14 3	13 6	
February 17	Glycerine 40	14 4	9 7	12 4
February 18	Glycerine 40	15 2	12 2	
February 19	Glycerine 40	13 5	13 6	
February 20	Glucose 40	13 5	21 1	
February 21	Glucose 40	12 2	12 2	16 4
February 22	Glucose 40	13 7	17 0	

Dog III Glycerine

Date	Carbohydrate fed	Excretion: Nitrogen	Excretion: Sugar	Sugar excreted average
February 11	Glucose 40	14 0	28 0	
February 12	Glucose 40	14 8	39 0	
February 13	Glucose 40	13 3	31 8	31 4
February 14	Glucose 40	12 0	31 2	
February 15	Glucose 40	12 7	25 5	
February 16	Glycerine 40	14 2	17 8	
February 17	Glycerine 40	14 3	28 0	25 7
February 18	Glycerine 40	13 9	30 8	
February 19	Glycerine 40	13 2	30 1	
February 20	Glucose 40	13 3	27 8	
February 21	Glucose 40	13 3	31 6	24 8
February 22	Glucose 40	12 5	15 2	

* Specimen lost.

administered is due to the logarithmic or enzymic action of insulin so clearly shown by Frank Allan (6) and the discrepancy occurs also with added glucose as the substrate It does not, in our opinion, justify the prescription of additional carbohydrate in the form of dihydroxyacetone for the diabetic patient whose pancreas is already working near the limit of its tolerance, to any greater degree than it justifies the prescription of additional glucose

Glycerine Glycerine is an alcohol and not a carbohydrate in the strict sense On account of its palatability and its food value it has been recommended for the treatment of diabetic patients Table 9 shows the results obtained on three of the dogs used in the preceding observations when this substance is substituted for glucose in the diet of depancreatized animals receiving constant doses of insulin In the observation on dog F there is apparently a greater excretion of sugar after the administration of glycerine than when glucose itself is given, but in those on the other two dogs the glucose excretion is approximately equal in the control periods and test periods There is a possibility that these differences are related to the nutritional condition of the animal in some way, the first dog (F) having a large amount of subcutaneous body fat while the other two dogs were merely well nourished animals There is no evidence, however, that in any of these animals, glycerine is preferentially metabolized as compared with glucose

DISCUSSION

Reviewing the foregoing results as a whole it can be concluded with confidence that there is no essential difference between the utilization of glucose and that of levulose, inulin, dihydroxyacetone or glycerine in depancreatized animals that are kept in a constant state of partial diabetes by the frequent injection of moderate doses of insulin The results are obviously more conclusive that those which it is possible to obtain with diabetic patients Even in the most extreme instances of this disease it is improbable that all of the insular tissue of the pancreas has become so destroyed that it can secrete no insulin, and in the vast majority of cases a considerable internal secretion of this hormone must still be possible And herein, in our judgment, lies

one important source of inaccuracy in the clinical observations which have hitherto been made concerning the preferential utilization of carbohydrate and related substances, for it is evident if any internal secretion of insulin occurs that it will vary from time to time, subject not only to dietetic and metabolic conditions, but also to nervous control When for any reason more insulin comes to be secreted there will result immediately, a better utilization of carbohydrate, and subsequently, when the secretion falls off again, an excess of glucose will appear in the organism because of the breakdown of the enhanced glycogen stores If these changes coincide with alterations in diet they may appear to be related to them

It is almost certain also that serious errors have been incurred in the interpretation of the clinical results on account of no allowance having been made for the fact, clearly demonstrated in this laboratory by Allan, that increase in the ingestion of carbohydrate in depancreatized animals receiving a constant amount of glucose, is not followed by a proportionate increase in the glycosuria As the amount of available glucose in the body increases in relation to insulin the glucose equivalent of each unit becomes greater and greater In the dihydroxyacetone experiments as already remarked, it is almost certain that a part of the absorbed substance is not immediately converted into glucose but is absorbed and retained for some time by the tissues so that a decrease in glucose excretion is to be expected

If, as we believe, these results are directly transferable to the patient the inference is that the attempt to use larger quantities of these substances than glucose itself, or other glucose precursors, will result in a strain on the patient's pancreas which will *eventually* succeed in decreasing his tolerance for carbohydrate 'Eventually' is used advisedly in this connection since it is well known that temporary excesses in carbohydrate are apparently well borne for a time Two mechanisms may be called upon to accomplish this Increasing the amount of carbohydrate (the substrate) may increase the amount of enzyme action of the available insulin as shown by Allan (6), or stimulation of the damaged pancreas may temporarily produce more insulin Probably both mechanisms occur, but in either case it is a sound principle not to require of a damaged organ its maximal activity

SUMMARY

A new method of studying the question of preferential met of certain carbohydrates or related substances is presentec consists in feeding to depancreatized animals receiving insulir quantities of the test substance in substitution for equal am glucose The results obtained by this method on levulose, dihydroxyacetone and glycerine afford no evidence that greater ties can be utilized by the diabetic organism than of glucos This suggests that these substances must pass through a gluco in their metabolism, and, therefore, do not undergo any pref utilization as compared with other carbohydrates The applic these results to the treatment of human diabetes mellitus is in

In conclusion, the writers wish to express their thanks to P Macleod for his kindness in providing facilities for this investi

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PULMONARY GAS DIFFUSION IN POLYCYTHEMIA VERA

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INTRODUCTION

The cause of erythremia, or polycythemia vera, has remained a subject for speculation ever since the clinical syndrome which goes under this name was described by Vaquez in 1892 (1) Christian (2) drew attention to the fact that many of the clinical symptoms are identical with those occurring in patients with severe anemia A more striking fact is that the symptoms very closely resemble those which are exhibited by many normal individuals after reaching high altitudes (3) The latter syndrome, which is called "mountain sickness," is now generally considered to be due to the lowered atmospheric oxygen tension In this condition, as in erythremia, an increase in the number of red cells in the peripheral blood is a most striking pathological feature In both diseases similar nervous symptoms occur Osler (4) in his early paper on polycythemia stated,—"the torpor, mental and physical, the sensation of fullness in the head, with headache, vertigo and in some cases nausea and vomiting, remind us of the symptoms to which mountain climbers and aeronauts are subject " Moreover in both conditions there may occur a similar train of visual disturbances, abnormalities of hearing, irritability, impairment of the higher mental faculties, especially memory and concentration, not infrequently insomnia, a sense of extreme weakness, particularly with unusual exertion, dyspnea, pains in the extremities, and very often attacks of syncope

The possibility that the cause of erythremia may in some way be bound up with insufficient oxygenation of the tissues has not received much support because studies have apparently indicated no abnormality in the oxygen carrying capacity of the hemoglobin (5), and

direct determinations of the percentage of oxygen saturation of the arterial blood in patients with polycythemia vera have yielded rather low, but still normal values A good many determinations of the total oxygen consumption under standard conditions have shown it to be usually normal or somewhat increased Studies of the blood gases, aside from the large oxygen content of the blood, corresponding to the increased hemoglobin content, are remarkable chiefly for the very small differences which appear to exist between the oxygen content of the arterial and of the mixed venous blood, in other words, in the low coefficient of oxygen utilization The blood appears to contain a large mass of circulating oxygen, which remains more or less fixed in the erythrocytes and does not readily flow out into the tissues

It was pointed out long ago by Paul Bert (6) that the physiological action of the blood gases depends upon their tension and not upon their concentration, and he predicted that the low oxygen tension existing at high altitudes would cause a polycythemia He confirmed this prediction in 1882 upon animals living at low barometric pressures (7) and in 1890 Viault (8) first demonstrated the changes which occur in man at high altitudes Direct determinations of the oxygen tension in freshly drawn blood have as yet been unsatisfactory in man, although the work of Krogh, who simultaneously determined the gas tensions in alveolar air and arterial blood in the rabbit (9), furnished data of great importance in clearing up the controversy concerning oxygen secretion in the lungs Nevertheless, the shape of the dissociation curve for oxyhemoglobin indicates that relatively large differences in tension may exist with very small changes in oxygen content, so far as blood equilibrated in vitro is concerned If we take the oxygen dissociation curve of normal blood, a difference of about twenty millimeters of oxygen tension out of a total of eighty may be found in the change from 95 to 90 per cent blood oxygen saturation We may inquire whether an obstruction to gas diffusion, either in the diffusion through the pulmonary tissue and the alveolar wall, or through some abnormality in diffusion into the erythrocytes, may lower the oxygen tension sufficiently in certain individuals to stimulate activity of the erythropoietic tissues

Pulmonary gas diffusion may be studied directly by the carbon monoxide method proposed by Krogh (10), and indirectly as is dis-

cussed below, by measurement of the changes in the oxygen content of the arterial blood when the blood flow is greatly increased, as during exercise

The principles which underlie the diffusion of gases in the lungs were formulated by Bohr (11), who suggested the use of carbon monoxide for the purpose of measurement Practical employment of this principle was made by Krogh and Krogh (12) and the possibilities and limitations of the method for clinical use and upon untrained subjects were explored and defined by M Krogh (10)

The method consists in measuring the diffusion of an essentially indifferent gas, carbon monoxide which is inhaled in low concentration and mixed with the pulmonary air of the subject Under such circumstances the gas combines practically at once with the hemoglobin, its tension in the blood in the lungs during the period of the experiment remaining so low as to be practically negligible The determination then consists in measuring the carbon monoxide tension in the alveolar air at the beginning and end of an accurately measured interval of time If C_0 is the concentration of carbon monoxide at the beginning and C_t is its concentration at the end of the time T, the quantity which passes per unit volume at any moment from alveoli to blood is proportional to the carbon monoxide tension of that moment and $\frac{\log C_0 - \log C_t}{T \log_b e} = k$ which is known as the *permeability* and is dependent upon the permeability of the alveolar membrane for gases

If k is multiplied by the pulmonary volume calculated at mid capacity, (V), and is divided by the barometric pressure less the tension of aqueous vapor at 37°C ($P - p$), we have the following expression, $\frac{k V}{P - p} = D_{CO}$, which is the *diffusion constant* for carbon monoxide, and which may be defined as the amount of carbon monoxide which will pass through the lungs as a whole per unit of time and per millimeter of pressure difference between alveoli and blood On the basis of certain assumptions based on the diffusion of gases through fluids, Bohr—and later Krogh—calculated from the data obtained for carbon monoxide, the diffusion constant for oxygen and other gases which are proportional to it. The diffusion constant so calculated for oxygen, D_{O_2} has a value equal to 1 23 D_{CO}

More than one hundred measurements of the diffusion constant made on twenty two normal subjects were published by Krogh The method was also utilized by Barcroft and his associates (13) during their Physiological Expedition to the Peruvian Andes for the study of the effects of high altitudes on man Determinations were made upon the eight members of the expedition both at sea level and after the climb to a point at approximately fourteen thousand feet above the sea and it appeared that the value so obtained for the diffusion constant bore a definite relationship to the severity of the symptoms of acute mountain sickness which each individual suffered in this small group

During the winter of 1921–1922 a systematic effort was made by one of us, with the courteous cooperation of the management of the Cerro de Pasco Copper Company to examine their employees prior to their departure for the group of mining camps of the company in the Cerro de Pasco district in the Peruvian Andes Our object was to ascertain whether a determination of the diffusion constant might be of any prognostic value in indicating the degree of mountain sickness to which a given individual was liable It was considered that it might be possible thus to detect individuals who were unfitted to reside for long periods at high altitudes A preliminary report was made in 1923 (14), as the results were distinctly encouraging, but it eventually became evident that no final conclusions could be drawn without more reliable and detailed clinical observation during the period of the actual disability of the subjects examined

Two papers have recently been published which have a bearing upon the reliability of diffusion measurements by the carbon monoxide method One relates to the completeness with which gas mixture occurs when an inhalation is made at the end of a maximal expiration Lundsgaard and Shierbeck (15) report that complete admixture depends on both the number and the depth of the mixing respirations, and doubts have been raised as to the completeness of gas mixture in such procedures as the present one We do not propose now to comment on this publication or upon the technique employed or the results reported We will, however, state that all of the determinations reported below were made after two or more deep rebreathing respirations, usually three, of at least two liters, commencing at the point of maximal expiration The technique, therefore, was practically identical with the method adopted by Krogh and Lindhard (16) for determinations of the circulatory minute volume in man by the nitrous oxide method The difficulty of this procedure for diffusion constant determinations lies in the fact that in the time required by the rebreathing, the rapidity of the diffusion of carbon monoxide may cause the concentration of this gas in the alveolar air to become rather low for accurate gas analysis This practical difficulty has been overcome by using a rather high initial percentage of carbon monoxide, somewhat over one per cent, and by giving the subjects sufficient preliminary training to enable them to make the initial mixing respirations deeply and rapidly

A second criticism may be found in the recent paper of Hartridge and Roughton (17), who conclude that the rate of combination of carbon monoxide with hemoglobin is not as rapid as had been previously assumed It is necessary, for the purpose of the diffusion constant determination, that the combination be sufficiently rapid to make the tension of the gas in the blood practically negligible If this is not so, and particularly if experiments are made in too rapid succession, so that the tension of the gas in the blood becomes considerable, appreciable error may result We have taken great pains to avoid repeated determinations, and all of the data reported below are based on experiments which are either the first experiment or the sole experiment of the day

STUDIES OF THE DIFFUSION CONSTANT IN POLYCYTHEMIA VERA

In view of the clinical similarity between the symptoms of polycythemia and those of cerebral anoxemia, particularly as manifested in residents at high altitudes, the writers have undertaken a study of the diffusion constant in seven patients with polycythemia vera The clinical protocols of these cases may be found at the end of this paper The determinations were made in the sitting position, at rest, and are summarized in table 2, which shows for each individual the average permeability (k) and the average diffusion constant for oxygen (D_{O_2}), as calculated at the normal mean capacity of the lungs Each of these

TABLE 1

Summary of published normal values for the permeability and diffusion constant

	K (permeability)			D_{O_2} (diffusion constant for oxygen)		
	Maximum	Minimum	Mean average	Maximum	Minimum	Mean average
Seventeen normal adults (Krogh)—men and women	8 0	5 0	7 3	43 3	27 1	35 6
Eleven normal adults* (Barcroft et al)—men	8 2	5 4	7 5	45 6	25 4	40 6

* It should be noted that the eleven adults measured by Barcroft and his associates were males whereas among Krogh s subjects were several women who in general have slightly lower diffusion constants than men, when compared per unit of surface area.

figures is the mean of at least two determinations upon each patient made upon different days

For comparison with the above data we have recalculated the average figures for normal individuals as found by Krogh, and by Barcroft and his associates

As is known, the pulmonary permeability in children is in general considerably greater than in adults, which compensates for the smaller lung capacity in young individuals and causes the diffusion constant, when calculated per square meter of body surface, to be approximately the same as that of the adult We have, therefore, taken only the figures for adults giving the maximum, minimum, and average figures to afford a comparison with the cases of erythremia, all in adults, studied as shown in table 2

It will be noted that the results of all of the determinations of the permeability (k) in the cases of polycythemia are much below the mean average of the normal cases as published in the literature, and that the diffusion constants as well are much below the mean average, and in all but two instances below the minimum values found in the twenty-eight normal cases The diffusion of gas through the lungs is determined by two factors, the permeability and the mean capacity of the lungs, and the diffusion constant is directly proportional to both In none of the above cases of erythremia is the total lung volume or the mid capacity abnormally low Indeed, the residual air (and hence the mid capacity) in most of the cases comprises an unusually

TABLE 2

Lung measurements and diffusion constant determinations in cases of erythremia

Case number	Sex	Age	Total capacity	Residual air	Residual air in percentage of total capacity	Measurements at mean capacity		
						K	D_{CO}	D_{O_2}
			liters	*liters*	*per cent*			
1	F	52	4 34	1 59	36 6	5 7	20 8	25 6
2	F	59	3 66	1 47	40 1	4 6	18 1	22 3
3	M	38	5 25	1 38	26 3	5 3	18 9	23 2
4	F	52	4 43	1 48	33 4	4 2	14 2	17 5
5	M	42	6 07	1 61	26 5	5 0	23 2	28 5
6	M	48	4 89	2 06	42 1	4 6	19 8	24 4
7	F	50	3 48	1 27	33 4	6 1	17 0	20 9

large percentage of the total capacity, as shown in table 2, and tends toward the relation which exists in pulmonary emphysema The abnormality, therefore, in these cases is due not to reduction in pulmonary volume, but to a lowered permeability which must depend either upon a reduced area of alveolar diffusing surface, or upon the thickness and individual peculiarities of this membrane Possible alterations of a like nature may exist, it is true, in the walls of the pulmonary capillaries or in the red blood cell membrane Through all of these three barriers the oxygen (or carbon monoxide) from the lungs must penetrate in order to effect its combination with the hemoglobin

THE EFFECT OF EXERCISE UPON THE ARTERIAL OXYGEN IN POLYCYTHEMIA VERA

The effect of an increased circulation rate and an increased oxygen consumption upon the oxygen saturation of the arterial blood, depends

TABLE 3

The effect of exercise on the oxygen capacity and saturation of the arterial blood in erythremia

	Pulse	Respiration	O_2 capacity	O_2 content	O_2 saturation
			vol. per cent	*vol. per cent*	*per cent*
Patient I					
Observations at rest	72	14	26 7	24 1	91
(Stationary running and hopping for 7 minutes. Patient became quite cyanotic and short of breath and exercise was terminated because of extreme weakness and vertigo)					
Observations immediately after exercise	136	34	26 3	23 5	89
Patient V					
Observations at rest	76	16	29 1	27 1	93
(Riding bicycle ergometer for 8 minutes. Color of face and hands became much deeper, and patient became quite short of breath. Did not feel marked fatigue)					
Observations immediately after exercise	140	38	29 1	25 4	87
Patient VI					
Observations at rest	76	16	22 4	21 3	95
(Vigorous bending and hopping for 5 minutes. Moderate cyanosis of lips, considerable shortness of breath weakness and vertigo)					
Observations immediately after exercise	120	30	22 2	20 1	90

on the rate at which oxygen can diffuse from the pulmonary alveoli into the blood The increased pulmonary ventilation during exercise will raise the alveolar oxygen tension, but will not suffice to supply the amounts required if the area of diffusing surface is not great

enough, or if the diffusion through that surface is not sufficiently rapid The matter can be tested by direct measurement of the arterial oxygen saturation during or immediately following severe exercise Earlier experiments (18) seemed to indicate that during exercise in man the arterial blood may not become completely saturated The recent study by Himwich and Barr (19) however, has indicated that in normal man, the arterial blood is as completely saturated with oxygen during exercise as during rest The saturation is, indeed, often appreciably augmented, notwithstanding the fact that there is at the same time a decided increase in the oxygen capacity

If we may assume that an impairment of pulmonary permeability exists in some cases of erythremia, as is indicated above, then it is quite possible that exercise in these patients, instead of increasing the arterial oxygen saturation, will diminish it Such studies have been made on three patients with erythremia, and the results are recorded below

It will be seen that in all of the three cases in which complete studies could be made, no increase in the percentage saturation of the arterial blood took place, and that in two a drop occurred, well beyond the limit of experimental error [1]

The question may be asked as to whether the slowed diffusion of gases in these cases of polycythemia vera may not in some way be due to the high erythrocyte count in the blood itself The writers think not because of the following considerations The available evidence[2] indicates that a low circulatory minute volume occurs in this disease This slowing of the pulmonary circulation should favor oxygen diffusion in the lungs, because a longer average loading time is afforded

[1] The blood oxygen determinations were made with the Van Slyke constant volume blood gas apparatus The figures quoted in table 3 represent the average of duplicate determinations, the maximal difference in which did not exceed 0 2 vol per cent (Van Slyke and Neill, J Biol Chem , 1924, lxi, 523)

[2] The early studies on the blood flow in polycythemia are unsatisfactory and contradictory Haldane suggested that a retarded circulation must be present, a view for which support may be found in the marked peripheral stasis shown to be present, notably by Brown and Giffin (23), and in the plethora found by various authors Liljestrand and Stenstrom (24) in carefully controlled studies with the Krogh-Lindhard nitrous oxide method have demonstrated considerable reduction

per corpuscle for taking up its moiety of oxygen The increased proportion of corpuscle volume to plasma will make a shorter distance between capillary wall and erythrocyte membrane for the diffusing gas to travel and will provide an increased area of red blood cell surface through which to penetrate From the study of the following case, there seems to be no significant change in diffusion of oxygen as a result of reduction in the number of erythrocytes and in the hemoglobin concentration

Case VII when first seen had an erythrocyte count in the peripheral capillary blood (finger) of 8 4 million and in the venous blood of 8 1 million Following two and one half months of intensive phenylhydrazine and radium therapy, marked diminution in the erythrocyte count occurred, so that a temporary period of anemia resulted the erythrocytes being 3 9 million in the finger blood and 4 0 million in the venous blood Determinations of the diffusion constant were made before and after this treatment with the following results

	RBC (per cubic millimeter) (Finger blood)	Capacity	Measurements at mean capacity	
			K	D_{CO}
	million	*vol per cent*		
Before treatment	8 4	27 8	6 1	17 0
After treatment	4 0	12 2	5 9	16 7

The diffusion constant was not altered, notwithstanding the change in the red cell count We are obliged, therefore, to conclude that the slow diffusion in this case is due to causes within the lung itself and not to the altered concentration of the blood circulating through it

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of the circulation rate in one case Serial determinations, to be published elsewhere, of the blood flow in an individual suffering from erythremia, under standard conditions of metabolism and posture during a course of treatment which reduced the polycythemia from eight to four and a half million red cells, showed a corresponding and coincident rise in the circulatory minute volume

This increased blood flow may have an important effect at the periphery The stagnation will be lessened, and the rate of flow through the peripheral capillaries will be increased The blood, though containing less oxygen and with a lowered oxygen capacity, may, with an increased rate of flow, deliver that oxygen to the tissues at a higher average pressure

DISCUSSION

At the present time the following opinions concerning erythremia appear to be widely held (20) It seems to be accepted that there is a constant increase, often very great, in the number of erythrocytes in the circulating blood, except during the periods when it is reduced by medical measures These erythrocytes are essentially normal in their morphology and physiological behavior There is a corresponding increase in the concentration of hemoglobin, which is also quite normal, at least so far as its oxygen carrying function is concerned The blood volume appears to be increased, the blood viscosity is increased in proportion to the degree of erythrocytosis, and the blood flow, if altered, is probably diminished The proposition is apparently accepted that the blood contains an amount of available oxygen greatly in excess of all tissue needs, and that therefore less than the normal amount is given off per unit of blood, although at the same time great stagnation occurs in the capillaries throughout the viscera and certainly at the periphery Nevertheless, with all of this excess of supposedly available oxygen, many of the clinical symptoms clearly resemble those of cerebral anoxemia The outstanding and constant pathological finding, aside from the generally increased blood content of the viscera, is the hyperplasia and hyperfunction of the erythropoietic tissues, a condition which can be reproduced in animals subjected to a low oxygen tension As far as the heart and lungs are concerned, some degree of pulmonary emphysema and chronic bronchitis is very common, although not a constant autopsy finding, and dilatation of the left heart and moderate cardiac insufficiency is frequent, but by no means invariable

The possibility that structural peculiarities of the pulmonary epithelium may exist, not directly related to circulatory disturbances, which are of such a nature that they may impede the pulmonary diffusion of gases in polycythemia vera is not inherently improbable There is some evidence that a lowered functional capacity of the lungs for gas diffusion may be an inherited characteristic, occurring in other individuals of the same family On the other hand, recent papers emphasize more and more the familial tendency of many cases of erythremia (21) When specific search has been made, high ery-

throcyte counts and splenomegaly have been reported in relatives who suffer from no lack of well being whatever

On the other hand, an inspection of the published data and a consideration of established clinical facts indicates that individuals vary widely as to the extent to which increases in erythrocyte count and hemoglobin are produced by exposure to low oxygen tensions The degree of erythrocytosis which is produced in conditions of chronic dyspnea caused by pathological changes in the circulatory and respiratory organs is known to vary considerably in different individuals, and the same variable response is found in normal persons subject, at high altitudes, to a low oxygen tension That the duration of the exposure has an effect is readily seen in the three groups of individuals studied by Barcroft and his party at Cerro de Pasco The recent arrivals (two weeks) had the smallest average increase above normal, the group of white residents who had lived at high altitudes for a year or more had a greater response, while the natives, who had lived all their lives in the high Andes, exhibited, on the average, the highest red cell counts and hemoglobin concentrations of all The studies which have been made upon animals also indicate wide individual variation in the erythropoietic response to a given lowering of oxygen pressure (22)

It is becoming increasingly evident that the disease, erythremia, or rather an erythrocytosis which precedes it, is likely to have been present for a long time before it finally obtrudes itself upon the consciousness of the patient Cases are cited of individuals who have applied to their physician for cosmetic reasons, to be rid of the unnatural red flush of the skin—"mehr rot als krank"—and who are otherwise symptom free The malady is one of middle life, when the development of secondary lung changes, fibrosis or emphysema, or of mild circulatory changes, or of hypertension, or of arteriosclerotic changes in the brain, may be the culminating event which finally impresses on the mind of the sufferer the consciousness of a serious disorder Nervous symptoms are among the most common for which medical advice is sought, and it is these symptoms which are common in mild grades of chronic anoxemia

It is, of course, possible that the slowed rate of diffusion of gas through the pulmonary epithelium, which we have shown to exist in these cases of polycythemia, may not be a causal factor, but after all,

an effect The possibility exists that the marked engorgement of the lungs with blood over a long period, a condition which these organs share in common with all of the other viscera, may produce alterations, structural or functional, the importance of which upon pulmonary gas exchange we have no means of estimating Studies of diffusion in heart and lung diseases, owing in large part to the technical difficulties, have been meager and the results rather uncertain, but in the cases which Krogh reports of asthma and pulmonary emphysema, no marked changes in the diffusion were observed

Comment must be made upon a final point We have stated that reduction of the erythrocyte count and hemoglobin does not appear to alter the rate of pulmonary gas diffusion How then can we account for the clinical improvement which often follows therapy directed to this end? The writers are inclined to attribute it to the reduction in the abnormally high blood viscosity, which appears to be associated in this disorder with a diminished blood flow, and to the resulting improvement in the circulation and in the supply of oxygen at a higher tension at the periphery

SUMMARY

1 Attention is drawn to the fact that although the blood in patients with polycythemia vera carries an amount of oxygen greatly in excess of that in normal blood, the symptoms in many respects resemble closely those produced by chronic anoxemia, particularly as seen at high altitudes

2 The slow insidious development of the symptomatology of the syndrome, the probable long standing antecedent polycythemia, the familial tendency of certain investigated cases, and the appearance of the disease as a disabling condition usually late in middle life, point to the cumulative effects of a long standing or inherited physiological fault

3 Evidence is presented to show that some functional obstruction exists in the lungs which lowers the pulmonary permeability for gases

4 Substantiating evidence is presented to show that where the pulmonary diffusing mechanism is put to a test, as in the increased blood flow during severe exercise, the oxygen content of the arterial blood falls, whereas in the normal individual it is increased

5 The disease cycle in these cases is pictured as follows There is an obstruction to the pulmonary diffusion of oxygen which produces a lowered oxygen tension in the bone marrow, and causes an increased erythrocyte production The resulting polycythemia, probably chiefly by reason of the increased viscosity of the blood, diminishes the blood flow This diminished blood flow, together with the lowered oxygen tension of the blood, produces a certain grade of anoxemia which manifests itself especially in the brain and nervous tissues The clinical improvement following reduction of the polycythemia and the coincident lowering of the blood viscosity, is produced by the increased blood flow at the periphery

Case I E M C female, age 52 housewife Admitted J H H, February 19, 1926 Discharged April 19 1926

Family and *past histories* have no obvious bearing on present condition

Onset of symptoms dates from June 1918, when she was thought to be "white" and "pale" A physician called her anemic and prescribed iron A year later she was observed to have purple lips and her friends remarked that her face had become flushed At the same time she commenced to have severe headaches, vertigo and fullness in the head, and bright spots before the eyes Examination by a physician in 1920 showed an erythrocyte count of 8 0 million Her symptoms continued as above described, and later on she had attacks of hematemesis, bloody diarrhea and epistaxis For the past eighteen months she has been especially troubled with roaring in the ears and head, with severe visual disturbances and there have been several syncopal attacks preceded by prodromal roarings in the ears, dizziness and dimness of vision She has become "clumsy," and falls easily There have been numerous paresthesias—tingling of the fingers and toes, numbness in the extremities, a burning sensation over the soles of the feet, and fleeting pains in the arms and legs There has been loss of memory and increasing emotional instability She has had extensive treatment with phenyl hydrazine, recently in large doses as the drug has clearly grown less effective in lowering the erythrocyte count There have also been repeated venesections and two radium treatments The erythrocyte count has fluctuated with treatment during the course of the disease the highest count, in June 1925, being 11 5 million

Physical examination February 1926 reveals a fairly well nourished and developed woman with dusky red flush to face, neck and hands. The lips, tongue and mucous membranes are a dark intense red The heart and lungs reveal no particular abnormalities B P 138/86 The spleen is enlarged, about three fingers below the rib margin The liver is not felt

Blood examination, February 28, 1926 R.B C 9 7 million W B C 27,000

Blood examination July 7 1926 (at end of period of observation) R.B C 6 1 million (vein), 6 2 million (finger)

Case II B U C, female, age 59, housewife Admitted J. H H, May 19, 1926 Discharged June 15, 1926

Family history She comes of a family in which obesity is common

Past history is negative except that the patient has always been obese, weighing at the maximum, fifteen years ago, 220 pounds

Onset of symptoms has been gradual Five years ago she began to suffer from headache, roaring in the ears, vertigo and occasional epistaxis, some blurring of vision, and on one occasion temporary blindness She was told then that she had high blood pressure About a year ago the left great toe became very tender and painful with burning sensations, and a few months later the great toe on the other side was similarly affected The process spread to the other toes—severe burning and reddening, intermittent, relieved by cold applications and elevation, aggravated by heat and lowering

Physical examination, May 1926, shows a moderately obese woman There is nothing very striking in the color of the face or chest The mucous membranes are engorged—cyanotic rather than erythremic The toes are bluish in color with marked color changes on application of heat or cold, or upon change in position The heart and lungs show no striking abnormality B P 185/110 There is moderate peripheral arteriosclerosis The spleen is felt just below the costal margin X-ray of chest shows slight enlargement of the left cardiac border

Blood examination R B C 7 7 million (finger), 8 2 million (vein) W B C 28,000

With three courses of phenyl hydrazine the symptoms in the feet were greatly relieved and the erythrocyte count became normal

Case III J T, male, age 38, fireman Admitted J H H, April 4, 1923 Discharged April 17, 1923

Family and *past history* negative

Symptoms of the present disease began about five years ago with attacks of dimness of vision, especially in the right eye, numbness in the arms and legs, dizziness, insomnia, weakness, and thickness of speech There has also been a sensation of fullness in the head, tinnitus, occipital headaches, and pain in the abdomen with occasional vomiting, and shortness of breath on exertion A year, or even two years prior to the definite onset of the above symptoms, however, he had noticed that his skin was becoming increasingly red

He was admitted to the hospital in April 1923, with the typical color of erythremia, dilatation of veins in pharynx and fundi, and a palpable spleen B P 190/110

Blood examination R B C 8 7 million W B C 11,300

The erythrocyte count at this admission reached as high as 9 4 million He was given several venesections and radiation once

He has been seen frequently since in the Out Patient Department and returned for observation and study in May, 1926 He has been able to do some light work and in general his symptoms have improved

Case IV C E , female, age 52 housewife Admitted J H H , December 8, 1925 Discharged February 20, 1926

Family and *past history* negative

Onset about six years ago with shortness of breath and dizziness especially on exertion About a year later she complained of pain in the chest and arms, morning headaches, attacks of abdominal pain and swelling, and redness and pain in the fingers and toes especially on the left side. During the past year she has had palpitation, one attack of severe pain in the left side, and several attacks of numbness of the arms and legs There has been some dimness of vision She has felt dull and her memory has grown poor

Physical examination, December 1925, shows moderate cyanosis of lips and face. The chest is slightly emphysematous with some cardiac enlargement. B.P 180/105 The measurements of a teleoroentgenogram of the heart are M R 4.5 cm., M.L 10 cm The eye grounds show moderately engorged veins The spleen is palpable and the liver edge just felt There is moderate peripheral arteriosclerosis

Blood Examination, December, 1925 R.B C 8 6 million W.B C 9,200 Arterial oxygen saturation 22 65/25 5 = 89 per cent

With phenyl hydrazine treatment and venesection the R.B C. dropped to 4 million, and the pains in the arms and legs improved At the period of this study (May, 1926) the blood showed R B C. 5 7 million and W.B C 10,000

Case V R F , male age 42, teacher Referred for study by Rockefeller Hospital, New York City

Family history The father had a florid complexion when younger, but a recent blood count was normal

Past history The patient has always had a ruddy complexion, undoubtedly above normal.

Onset about 7 years ago when he was disturbed by transient bright specks in both fields of vision, later diplopia, vertigo, nausea and vomiting—at times projectile—transient paresthesias transient aphasia and loss of memory, "thickness" of speech, and difficulty in the association of ideas. There have been occasional aches and pains in the extremities, usually not lasting, and infrequent occipital headache About eighteen months ago there was a sense of fullness noted in the left side due to enlargement of the spleen

Physical examination May 1926, reveals a well nourished man with very dusky reddish skin and tortuous engorged temporal veins The eye grounds show marked deepening of the general retinal color with thick distended veins, and general vascular engorgement The mucous membranes, tongue and lips are dusky red The lungs and heart are clear and the x ray shows no abnormalities The liver edge is felt below the costal margin and the spleen, firm but not tender, descends two fingers below the rib border B.P 130/100 The erythrocyte count in the past two years has been as high as 12 9 million There have been numerous courses of phenyl hydrazine He has also received X ray treatments and venesection

Blood examination R.B C 7 3 million (vein), 7.5 million (finger)

Case VI C R J, male, age 48, laborer Referred for study through the courtesy of Dr Thomas R Boggs

Family and *past histories* are negative

Onset of symptoms in the spring of 1924 with pain across the shoulders and lower back, progressive weakness and loss of weight, occasional nausea with vomiting, dizziness, headache and occasional vertigo He was first observed at Bay View Hospital in November, 1924, at which time in the physical examination it was noted that there were dilated blood vessels over the face and forehead, the chest was emphysematous in type, the heart was not enlarged B P 120/80 There was a very large and rather firm spleen The erythrocyte count was 7 2 million and the leucocytes 34,000 During the next eighteen months he received a number of courses of phenyl hydrazine in doses of from 0 1 to 0 2 gram per day The erythrocytes on several occasions rose to 8 5 million The blood pressure appears to have risen progressively following the first observation and in March, 1926 the mean of several observations was 200/120 Recently, phenyl hydrazine therapy has had decidedly less effect on the erythrocyte count than during the first months of treatment

Status praesens, June 1926, reveals a man of medium stature with evidence of considerable undernutrition There are many dilated venules on the nose and cheeks, the ears and lips are bluish red, and the dark color is very striking over the tongue, mucous membranes and conjunctivae The finger tips are distinctly cyanotic rather than red The eye grounds show marked venous engorgement The chest is moderately emphysematous The heart is somewhat enlarged to the left, the border percusses 14 cm from the mid line at the fifth interspace B P 158/100 There is well marked peripheral arteriosclerosis with especial thickening of the radial and brachial arteries The spleen is very large, extending 4 cm below the umbilicus, firm and not tender The liver edge is distinctly felt just below the costal angle

X-ray examination of the chest (Dr Baetjer) showed the teleoroentgenogram measurements of the heart to be M R 6 cm, M L 10 5 cm The chest x-ray plate showed the heart and aorta a trifle enlarged and an emphysematous type of chest

Blood examination R B C 7 07 million (finger), 7 4 million (arm vein)

Case VII S S, female, age 54, housewife Referred for study through the courtesy of Dr H M Thomas, Jr

Family history The patient has one brother who has always had a high color (An examination of this relative has not been possible)

Past history The patient has been distinguished by her ruddy complexion since childhood Her ears and nose have been especially deeply colored, so that she has been teased as being "rummy" This color has always been much worse on exertion

Onset was insidious with hot flushes 7 or 8 years ago at the commencement of the menopause period Later she had increasing weakness, fullness in the head

and giddiness, headache behind the eyes and pains in the back and legs with numbness and burning sensations in the feet and hands She was told by a physician 5 years ago that she had hypertension A year ago she had a sudden attack of vertigo followed by unconsciousness and there have been six or seven more such episodes since She has had palpitation and shortness of breath on exertion Her memory has become very poor, she cannot concentrate and she has become increasingly nervous and irritable She has lost seventeen pounds in weight in the past 6 years During the course of the past five months she has had two courses of phenyl hydrazine and several radium treatments

Physical examination shows a woman with ruddy complexion, deeply colored lips, tongue and mucous membranes There is evidence of moderate loss of weight. The heart is not enlarged and the sounds are normal Teleoroentgenogram measurements are M R 4 cm and M.L 9.5 cm The lungs are clear but hyperresonant The x ray indicates an emphysematous type of chest. B P 170/110 Very moderate peripheral arteriosclerosis There is a firm palpable spleen descending two fingers' breadth and the liver edge is felt The hands and feet are negative

Blood examination R B C 8 4 million (finger), 8 1 million (vein)

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and were able to recover the latter in pure culture from 26 cases These organisms were essentially identical with strains isolated from normal stools in their cultural characteristics, hemolysin production and pathogenicity They conclude that "if these bacilli are of etiologic importance in pernicious anemia it must be on the basis of their excessive numbers and activities, particularly at levels of the intestine where absorption is active and where they are commonly found only in negligible numbers" Cornell (10) has been able to produce anemia, loss of weight, convulsions, diarrhea and eventually death in rabbits by chronic infection with *B Welchii* The anemia though usually mild, is sometimes acute and profound In all cases it is characterized by anisocytosis, and he believes this to be due to the direct action of the toxin on the erythrocytes He states, "it is not unreasonable to imagine that pernicious amenia might be a chronic infection by *B Welchii*" Kahn and Torrey (11) by repeated intravenous injections of suitable amounts of potent *B Welchii* toxin in two monkeys have produced severe anemias of a type resembling pernicious anemia Both monkeys within 20 days developed an active immunity which rendered further injections of toxin inocuous in spite of increased dosage By repeated intramuscular injections of cultures and toxin of *B Welchii*, Patterson and Kast (12) were able to produce in rabbits severe to moderate anemias of secondary type accompanied by anisocytosis, polychromatophilia, poikilocytosis, and increase in nucleated red cells

The work reported in this paper agrees with that of Kahn in confirming the findings of Herter and Simonds Additional evidence is presented which suggests a somewhat different interpretation of the findings

EXPERIMENTAL

B Welchii spore counts The characteristic stormy fermentation produced in milk cultures by *B Welchii* was chosen as the means of determining the number of spores, and the method used was essentially a modification of one devised by Simonds (2)

Method The specimens were collected in the wards and brought to the laboratory All watery and enema stools were discarded Approximately all of the stool was broken up in a glass beaker in 500 cc of freshly prepared 0 9 per

cent salt solution by means of a glass rod One hundred cubic centimeters of the emulsion were placed in a bottle, tightly corked and shaken vigorously in a shaking machine for 30 minutes Another 100 cc. were transferred to a tared evaporating dish dried first on a steam bath and then in a desiccator and weighed The shaken emulsion was filtered through 10 thicknesses of sterile gauze to remove gross particles and approximately 10 cc transferred with a sterile pipette to the bottom of a sterile test tube measuring 250 x 27 mm The upper half of the tube was heated very hot in a Bunsen flame to eliminate accidental contamination The tube was then immersed at least to half its length, in a water bath at 80°C for 20 minutes, thus destroying all vegetative forms of bacteria One cc. of the heated emulsion was then transferred to a 250 x 27 mm tube containing 9 cc of sterile 0 9 per cent salt solution and another 1 cc. to a 150 x 16 mm tube containing about 10 cc of sterile skimmed milk which had just previously been heated in an Arnold sterilizer at 100°C for 10 or 15 minutes With a fresh pipette the 10^{-1} dilution was thoroughly mixed by blowing and similar transfers made Dilutions were carried often as high as 10^{-10} In cases with known high spore counts cultures of the lower dilutions were usually omitted.

The milk cultures were placed immediately in a Brown (13) anaerobic jar, anaerobiosis established, and the jar placed in the incubator at 37 5°C After 3 days incubation the jar was opened and those tubes were called positive which showed typical stormy fermentation with an odor of butyric acid and disclosed in stained smears Gram positive bacilli morphologically resembling *B Welchii* Occasionally coagulation of the milk occurred with or without a moderate number of gas bubbles In such instances 1 cc was transferred to a fresh milk tube and incubated as above, on the assumption that, if too few *B Welchii* were present in the original sample to produce stormy fermentation a sufficient number would be present in the transfer to bring about a definite result If only coagulation with or without a few gas bubbles occurred after 3 days incubation in the subculture the tube was considered to be negative Smears of such tubes invariably showed Gram positive bacilli which usually did not resemble *B Welchii* morphologically All of the original tubes showing no change in the milk were regarded as negative.

In calculating the number of spores it was assumed that the tube containing the smallest amount of emulsion necessary to produce stormy fermentation, either in the original or subculture contained one *B Welchii* spore It is conceivable that many more spores might be necessary Assuming the required number to be K, the number per cubic centimeter in an emulsion causing stormy fermentation as far as the 10^{-3} tube would be $1000 \times K$. However, if we assume $K = 1$, the numerical ratio remains the same for the various emulsions and this simpler expression has been used

With few exceptions stormy fermentation proceeded in an orderly manner, positive through a certain dilution and negative thereafter Occasionally the first negative tube was followed by a positive with the remainder negative In

TABLE 1

Case number	Diagnosis	Sex	Age	Date	Stool: State*	Stool: Age	Stool: Spore count	Stool: Vegetative count	Red blood cells	Hemoglobin	Gastric contents Free/Total: Fasting	Gastric contents Free/Total: ½ hour	Gastric contents Free/Total: 1 hour	Gastric contents Free/Total: 1½ hour	Remarks
						hours		$\times 10^3$	$\times 10^3$	per cent	cc	cc	cc	cc	
1	Pernicious anemia	M	66	May 9, 1924	F	—	740,000	—	1 3	26	0	0	0	0	
											—	—	—	—	Kaolin started June 6, 1924
				July 16, 1924	SS	3½	13,000	—	1 0	25					
				August 5, 1924	SS	4	1,300	600	1 4	23					Transfusion, 500 cc July 27, 1924
				August 18, 1924	SS	3	21,000	670	1 5	27					
				October 1, 1924	F	4	28,000	1,400	1 0	19					
				October 8, 1924	F	4½	24,000	400	0 9	19					
				October 16, 1924	F	2	300,000	180	0 7	19					
				October 30, 1924	F	5	13,000	400	0 7	17					
				November 6, 1924	SS	4	19,000	1,000	0 6	19					Kaolin stopped November 1, 1924
2	Pernicious anemia	M	51	June 10, 1924	—	4	90,000,000	—	1 3	29	0	0	0	0	Kaolin started June 6, 1924
											3	6	5	8	
				June 24, 1924	SS	4	53,000,000	—	1 2	29					
				June 30, 1924	SS	5½	100,000,000	180	1 1	29					
				July 22, 1924	F	7	2,400,000	1,400	1 1	22					Kaolin stopped July 10, 1924
				July 29, 1924	SS	9	300,000	1,000	1 4	24					

				September 12, 1924	F	4	17 000,000	1,400	1 8	29					Transfusion 500 cc. August 27, 1924
				September 26, 1924	F	5	1 200 000	600	1 5	28					
				September 30 1924	F	8	19 000 000	940	1 4	25					
				October 7 1924	F	9	1 200,000,000	440	0 9	20					
				October 16 1924	SS	5	260 000 000	1,100	1 2	26					
				October 21 1924	F	4	17 000 000	700	1 1	21					
				October 28 1924	F	6	>1 000,000	500	1 0	23					
				November 4 1924	F	8	128 000 000	590	1 1	24					
				November 11, 1924	F	2	1 100 000	1,000	1 3	25					
				December 18, 1924	SS	4	200 000	—	1 1	24					
				January 23, 1925	SS	6	21,000 000	—	1 0	22					
				March 31 1925	F	8	17,000,000	—	2 4	34					
3	Pernicious anemia	M	57	June 10, 1924		5	3,500 000	—	1 0	29	0	0	0	0	Kaolin started June
											2	4	4	5	6 1924
				July 2 1924	SS	4	200	4 000	1 0	18					Transfusion, 500 cc. June 21 1924
				July 17 1924	SS	9	45 000	910	0 9	18					
				January 29 1925	SS	7	33 000	—	0 9	19					Practically no kaolin
4	Pernicious anemia	M.	62	July 7, 1924	SS	3	220,000,000	1,200	1 8	46	0	0	0	0	
											5	0	10	10	
				July 22, 1924	SS	4	80 000 000	3 000	1 7	45					
				July 29 1924	F	8	17 000,000	1 200	1 9	47					
				August 12, 1924	F	4	<190,000	220	2 1	48					
5	Pernicious anemia	F	46	July 22, 1924	SS	4	2,300 000	180	1 5	34	0	0	0	0	
											3	1	1	1	

* F = formed, SS = semi-solid.

TABLE 1—*Continued*

Case number	Diagnosis	Sex	Age	Date	Stool: State*	Stool: Age	Stool: Spore count	Stool: Vegetative count	Red blood cells	Hemoglobin	Gastric contents Free/Total: Fasting	½ hour	1 hour	1½ hour	Remarks
						hours		× 10³	× 10⁶	*per cent*	*cc*	*cc*	*cc*	*cc.*	
6	Pernicious anemia	M	65	August 18, 1924	SS	3	77,000,000	150	3 1	57	0/—	0/—	0/—	0/—	
				March 25, 1924	SS	5½	8,300,000	—	1 2	25					
7	Pernicious anemia	F	33	September 17, 1924	SS	6	500,000	1,700	2 1	52	0/4	0/3	0/6	0/4	
				September 19, 1924	Γ	6	9,800,000	—	2 5	60					
				September 26, 1924	F	5	77,000,000	150	2 6	67					
				October 14, 1924	F	5	>30,000,000	1,100	2 5	67					
8	Pernicious anemia	M	51	September 30, 1924	SS	9	210,000	1,200	1 5	52	0/—	0/—	0/—	0/—	
				October 8, 1924	SS	5	780,000	1,200	2 6	69					
				October 14, 1924	SS	4	3,700,000	1,100	2 2	70					
				October 29, 1924	SS	4	240,000	800	2 7	71					
				November 4, 1924	SS	8	>13,000,000	1,200	2 0	70					
				November 11, 1924	SS	6	200,000	3,000	2 3	70					
9	Pernicious anemia	M	40	January 29, 1925	SS	7	500	—	0 9	24	0/3	0/6	0/0	0/5	
				March 31, 1925	F	8	1,300	—	1 1	26					
				May 2, 1925	SS	4	630,000	—	1 2	25					

10	Pernicious anemia	F	48	April 27 1925	F	5	500	—	0 9	25	0	—	0	—
				May 7 1925	F	4	1 900	—	1 0	22	9	—	14	—
				May 12 1925	SS	6	>3 000 000	—	0 7	21				
11	Pernicious anemia	M	33	May 2 1925	SS	4	2 300 000	—	0 9	20	0	0	0	0
											—	—	—	—
12	Rheumatic fever	M	40	June 6 1924	—	—	77	—	—	88				
13	Rheumatic fever	M	40	June 6 1924	—	—	5 000	—	—	—				
14	Diabetes	F	22	June 26 1924	SS	6	65	—	—	—				
15	Diabetes	M	32	September 17 1924	F	4	6 700	—	—	—				
16	Chronic nephritis secondary anemia	M	29	March 23 1925	F	6	4 350	—	4 6	65				
17	Chronic nephritis, hyperten sion	F	29	April 27 1925	F	5	7 800	—	4 4	88				
18	Ulcerative colitis	M	35	April 27 1925	SS	5	<910	—	—	—				

TABLE 1—*Concluded*

Case number	Diagnosis	Sex	Age	Date	Stool				Red blood cells	Hemoglobin	Gastric contents Free/Total				Remarks
					State*	Age	Spore count	Vegetative count			Fasting	½ hour	1 hour	1½ hour	
						hours		$\times 10^6$	$\times 10^6$	*per cent*	*cc*	*cc*	*cc*	*cc*	
19	Peptic ulcer, secondary anemia	F	52	June 2, 1925	F	8	20,000	—	3 2	48					
20	Normal	M	25	August 28, 1924	F	4	240	5,300	—	—					
21	Normal	M	29	August 28, 1924	F	2	350	1,100	—	—					
22	Normal	M		September 9, 1924	F	7	230	320	—	—					
23	Normal	M	32	September 9, 1924	F	1	50	1,200	—	—					
24	Normal	M	28	September 12, 1924	F	1	290	4,200	—	—					
25	Normal	M	29	September 23, 1924	F	2	260	2,000	—	—					

such an instance the first negative tube was regarded as the last positive, on the assumption that the one spore, or "K" spores, necessary to cause stormy fermentation had by chance been carried over into the next dilution

To compensate for the varying water content of the stool, the results can be expressed as suggested by Simonds, as "spores per gram dried stool" The calculation is simple, for example

10^{-6} = last positive culture

2 5 grams = weight dried stool in 100 cc. emulsion

$$\frac{100}{2.5} \times 10^{6} = 40{,}000{,}000 = \text{spores per gram dried stool}$$

In table 1 are tabulated the spore counts in stools from 11 cases of pernicious anemia, 8 cases of miscellaneous disease, and 6 normals Fifty-four individual counts were made on the 11 cases of pernicious anemia The averages for all counts in each group are 46,000,000, 3400 and 240 per gram of dried stool respectively These figures confirm the findings of previous workers, namely, that *B Welchii* spores are markedly increased in stools from cases of pernicious anemia

Simonds (2) found that *B Welchii* spores in stools from normal individuals were greatly increased during diarrhea For this reason objections might be raised as regards the reliability of the results because of the varying water content of the stools As previously stated, all diarrhea stools and enema stools were discarded It seemed to make no difference whether the stools were semisolid or formed For example, in case 2, the samples described as formed gave counts ranging from 1,100,000 to 1,200,000,000 and those described as semisolid gave counts varying from 200,000 to 260,000,000

As the period of time from passage of the stool to dilution varies from 1 to 9 hours it is conceivable that this might have considerable influence on the results One might expect an increase in the number of spores as the interval was prolonged As a matter of fact, in 6 of the 9 cases of pernicious anemia in which two or more specimens were examined the average of counts with long intervals was somewhat lower than that of those with short intervals

If the disease, pernicious anemia, is caused by chronic intestinal infection with *B Welchii*, and if the spore counts are indicative of the numbers of vegetative or active forms of the bacillus, one would expect to find high counts during relapses and low counts during

remissions, particularly as Kahn and Torrey (11) have shown experimentally that the blood changes in monkeys following intravenous injection of *B Welchii* toxin are rapid In cases 4 and 10 such a relation seems to exist In the former there is a marked decrease coincident with clinical improvement, whereas in the latter the reverse is true In cases 6 and 7, however, the highest counts are found during periods of relative or absolute remission, and the lowest counts during periods of relative or absolute relapse These findings seem to indicate that there is no definite relation between the spore counts and the clinical condition of the patient

In the first three cases an attempt was made to produce clinical improvement by the administration of kaolin, on the assumption that pernicious anemia might be due to chronic intestinal infection with *B Welchii* Walker (14) states that kaolin, as a spray, has been used successfully in Germany in the treatment of faucial diphtheria, and, by ingestion, has been employed for ptomaine poisoning and dysentery, Braafladt (15) showed that kaolin is capable of rendering innocuous appreciable amounts of dysentery, botulinus and diphtheria toxins in vitro, and Eyre (16) observed that large amounts of diphtheria and dysentery toxins are removed by filtering through kaolin filters Braafladt also found that *B Welchii* spores could be eliminated from normal stools by feeding kaolin, although the importance of the observation is somewhat diminished by the fact that the maximum amount cultured was only equivalent to approximately 0 0001 gram dried stool Kaolin was given daily, just before retiring, in 30 gram amounts in orange juice In this series treated with kaolin, cases 1 and 3 showed a decided reduction in the number of spores In case 2 treatment had little if any effect The typical clinical course of the disease was apparently not influenced in the slightest by the spore reduction in cases 1 and 3

In the routine cultures of stools from diseases other than pernicious anemia several spore counts were made on 2 cases of relatively mild secondary anemia All of the samples gave high spore counts, and an attempt was made to account for the apparent discrepancy Both cases were known to have gastric achylia The achylia and the anemia seemed to be the only features in common with cases of per-

nicious anemia In order to determine the ruling factor, a number of cases of secondary anemia were selected for study, some with and others without gastric achylia The results, as tabulated in table 2, were startling The average of all spore counts on the stools from the cases with achylia, cases 26 through 30, was 51,000,000, whereas in the cases without achylia, cases 31 through 36, the average was 1200

Vegetative B Welchii counts If *B Welchii* is to be considered as an etiological factor in pernicious anemia, some effort should be made to estimate the number of active or vegetative forms of this organism in the gastro intestinal tract Obviously this would be most difficult to accomplish by cultural methods, because of the presence of overwhelming numbers of other bacteria The morphology of *B Welchii* is fairly characteristic when stained by Gram's method, but it is, of course, impossible to distinguish between them and certain others of the less common sporulating anaerobic bacilli In view of the fact, however, that Kahn (8) and Moench, Kahn and Torrey (9) found that *B Welchii* were the only sporulating anaerobes which could be recovered consistently from the stools of pernicious anemia patients, it was felt that a simple counting of the forms morphologically resembling *B Welchii* might furnish valuable information

Method With a wax pencil a line was drawn across a clean glass slide 20 mm from one end On the area (20 x 25 mm) marked off were placed 9 loopfuls of distilled water A loopful of the shaken stool suspension, after filtering through gauze, was mixed with the 9 loopfuls of water and spread out as evenly as possible over the area The same loop (3 mm in diameter) was used for all of the transfers The smear was allowed to dry in the air It was then fixed by heat and stained by the Gram method As *B Welchii* is extremely Gram "fast," decolorization with alcohol was carried on about twice as long as usual No counterstain was used

For microscopic examination a mechanical stage was used and 12 fields, each 5 mm apart were examined All fat, short to medium length bacilli occurring singly, or rarely in pairs were included in the count. Extremely long and relatively slender forms were not included The total number in all fields divided by 12 gave the average per field With a tube length of 16 0 cm the diameter of the oil immersion field was 0 15 mm The volume contained in 1 loopful was determined by weighing the loop with and without distilled water, and found to be 0 0012 cc Assuming for example, that the total count of the 12 fields was 5,

TABLE 2

Case number	Diagnosis	Sex	Age	Date	Stool: State*	Stool: Age	Stool: Spore count	Stool: Vegetative count	Red blood cells	Hemoglobin	Gastric contents Free/Total: Fasting	½ hour	1 hour	1½ hours	Remarks
						hours		$\times 10^6$	$\times 10^6$	*per cent*	*cc*	*cc*	*cc*	*cc*	
26	Hemorrhoids, secondary anemia, achylia gastrica	M	46	June 30, 1924	SS	2	14,000,000	1,500	4 5	70	0/6	0/13	0/6	0/25	
				December 18, 1924	F	2	5,000,000	—	5 6	84					
27	Arteriosclerosis, lues, Paget's disease, achylia gastrica	M	50	November 12, 1924	SS	5	1,300,000	800	4 1	62	0/8	0/7	0/11	0/8	
				November 20, 1924	SS	2	27,000,000	920	—	—					
28	Secondary anemia, achylia gastrica	F	57	April 17, 1925	SS	4	210,000,000	—	4 5	36	0/20	—/—	0/12	—/—	
29	Scurvy, secondary anemia, achylia gastrica	M	73	May 7, 1925	F	4	>1,500,000	—	5 0	45	0/4	0/8	0/7	0/7	
30	Carcinoma of stomach, secondary anemia, achylia gastrica	M	54	June 6, 1925	SS	5	>100,000,000	—	4 2	40	0/2	0/1	0/1	0/2	

31	Secondary anemia tuberculous peritonitis (?)	F	72	February 25, 1925	SS	5	43	—	3 4	32	— —	— —	— —	— —	Vomitus = free HCl
32	Carcinoma (hepatic flexure of colon) secondary anemia	M	60	April 23 1925	SS	4	260	—	3 6	36	0 0	4 79	— —	— —	
33	Echinococcus cyst of liver, secondary anemia	M	59	May 7 1925	SS	4	1 600	—	3 4	64	0 10	0 25	5 27	7 30	
34	Sprue anemia	M	45	May 9 1925	SS	5	4 400	—	1 0	25	10 16	— —	— —	— —	
35	Tertiary lues acute cholecystitis secondary anemia	M.	48	May 12 1925	SS	6	360	—	4 1	67	4 13	10 20	8 33	27 34	
36	Pulmonary tuberculosis broncho-pneumonia secondary anemia	M	42	June 2 1925	SS	8	360	—	3 3	55	0 3	8 15	14 18	10 16	

* F = formed SS = semi-solid.

the average count per field would be $\frac{5}{12}$ and the count of a stool which contained in suspension 5 0 grams per 100 cc would be calculated as follows

$$\text{Area of field} = \left(\frac{0\ 15}{2}\right)^2 \pi = 0\ 0176 \text{ sq mm}$$

$$\text{Area of smear} = 25 \times 20 = 500 \text{ sq mm}$$

$$\text{Fields per smear} \frac{500}{0\ 0176} = 28{,}000$$

$$\text{Count per loop} = \frac{5}{12} \times 28{,}000 = 12{,}000$$

$$\text{Count per cc} = 12{,}000 \times \frac{1}{0\ 0012} = 10{,}000{,}000$$

$$\text{Count per gram dried stool} = (10 \times 10^6) \times \frac{100}{5} = 200 \times 10^6$$

The results of the vegetative counts are given in tables 1 and 2 The average of 36 stools from cases of pernicious anemia was 1000×10^6 and of 3 stools from cases of gastric achylia 1100×10^6 Counts of six normal stools averaged 2400×10^6 In the 39 pernicious anemia and achylia specimens there were only 3 giving counts higher than 1700×10^6, whereas in the normals 3 out of 6 were higher than this figure Undoubtedly many of the organisms counted were dead This applied, however, to both sets of figures, and furthermore, even though the bacilli were dead, the count would seem to be indicative of the actual number of live organisms high up in the actively absorbing portions of the intestinal tract Although it must be acknowledged that the method is very crude, the figures are sufficiently accurate to show that normal stools contain at least as many, probably more, vegetative forms of the sporulating anaerobic bacilli as stools from cases of pernicious anemia and gastric achylia

DISCUSSION

It has always been possible to demonstrate the presence of *B Welchii* spores in stool specimens regardless of their source in the amounts used for culture Confirming the work of several other investigators it has been shown that in pernicious anemia these spores are usually increased to a marked degree

On the basis of the last observation, together with the blood changes

brought about either by the intravenous injection of *B Welchii* toxin (Kahn and Torrey (11)), or by chronic *B Welchii* infection (Cornell (10)), it has been suggested that chronic intestinal infection with *B Welchii* may very possibly be the cause of pernicious anemia Is it fair to assume that because of an increased spore count there is an accompanying increase in vegetative or active forms? All other things being equal such might be the case The ratio of spores to vegetative forms in stools from cases of pernicious anemia is 1 20, whereas in normal stools, assuming that 50 per cent of the vegetative forms are *B Welchii*, the ratio is 1 5,000,000 This extraordinary difference would seem to indicate that in pernicious anemia some change has taken place in the gastro intestinal tract which either favors spore formation, inhibits growth of the organism or combines these two possibilities In view of the fact that in both instances the vegetative counts are approximately the same, it seems more logical to assume that the marked increase in spores is due to some change in the gastro intestinal tract favorable to spore formation

B Welchii, unlike the majority of the other anaerobic bacilli belonging to the same group, such as *Vibrion septique*, *B edematiens* *B sporogenes* and *B histolyticus*, does not readily produce spores For their formation in culture media a slightly alkaline reaction is essential In media containing fermentable sugars, and hence variable amounts of acid, spores are rarely formed Simonds (2) found that *B Welchii* spores were not formed in sterilized adjusted fecal suspensions inoculated with either pure *B Welchii* cultures or mixtures containing *B Welchii* and *B coli* or *B subtilis*, provided the acidity of such suspensions was equivalent to 1 0 per cent normal hydrochloric or acetic acid (phenolphthalein used as indicator) Furthermore, in unsterilized fecal suspensions known to contain *B Welchii*, and to which were added 1 0 per cent of various fermentable sugars (lactose, maltose and saccharose), *B Welchii* spores were not found provided the final acidity was greater than 4 0 per cent Expressed in terms of hydrogen ion concentration it will be found that a 10 per cent fecal suspension adjusted to 1 0 and 4 0 per cent acid (normal HCl), using phenolphthalein as an indicator, will have a pH of approximately 7 5 and 5 0 respectively

Cannon (17), in his studies on normal persons and rats, observed

that a diet relatively rich in carbohydrates results in an aciduric fecal flora with an accompanying decrease or absence of *B Welchii* spores Cannon and McNease (18) studied the reaction and flora of the cecum and colon of white rats on meat and on meat and lactose diets On the former diet the intestinal contents were foul in odor, had a pH of 7 0–7 1 and contained a flora predominantly proteolytic, forming gas in deep Viellon tubes of whey agar When lactose was added to the diet the offensive odor disappeared, the acidity of the contents increased (cecum = pH 4 5 and colon = pH 5 7), the flora became predominantly aciduric and the Viellon tubes usually showed no gas production A corresponding increase in acidity of the cecal and colonic contents accompanied by a shift from proteolytic to aciduric flora was observed in white rats by Hudson and Parr (19), when a diet rich in carbohydrates was substituted for one containing meat By feeding kaolin Braafladt (15) brought about a similar shift from the normal proteolytic flora of man and dogs to a flora of the aciduric type accompanied by a marked quantitative decrease in *B Welchii* spores Hines (20), in studying the intestinal flora in diarrhea noted a marked increase of *B Welchii* spores in the diarrheas characterized by a proteolytic flora, and either an absence (2 cases) or a normal number (1 case) of spores in those with an aciduric flora

The various observations mentioned above would seem to indicate that the reaction of the gastro-intestinal contents is an important factor in *B Welchii* spore formation In conditions accompanied by an aciduric flora and by an increase in acidity of the intestinal contents there is a marked decrease in the number of *B Welchii* spores Moench, Kahn and Torrey (9), on the basis of their study of the intestinal flora in cases of pernicious anemia, have concluded that the flora is non-proteolytic in type Such a conclusion seems hardly justifiable, for in the 16 cases, in which the colonies on acid whey agar were identified, the *B coli*-*B acidophilus* ratio appears to average 94 to 6 Furthermore, the usual characteristics of stools from cases of pernicious anemia, such as, foul odor and the presence of large amounts of undigested vegetable material, suggest a flora of the proteolytic type This inhibitory effect of acidity on sporulation and the marked increase of *B Welchii* spores in stool specimens from cases of gastric achylia, with or without pernicious anemia, suggest that the increase

may be secondary to the achylia, i e , the result of changes in reaction favorable to sporulation brought about in some portion of the gastro intestinal tract by the absence of normal gastric juice

Very little is known concerning the reaction of the content of the normal small intestine Some of the standard text books state that it is slightly alkaline and others that it is acid The average of 9 electrometric determinations in 3 normal subjects by Long and Fenger (21), which were made within 6½ hours after normal meals and when the tip of the Rehfuss tube was shown by x-ray to be beyond the duodenal jejunal junction, was pH 5 83 Apparently no precautions were taken, however, against loss of CO_2 in transportation of the specimens from the clinic to the laboratory, and measurements were made in a type of electrode (Hasselbalch) which would further tend to dilute the CO content Above pH 5 5 such a loss would undoubtedly decrease the acidity The most accurate observations are those of McClendon, Bissell, Lowe and Meyer (22) Two normal subjects (age about 25) were studied for a period of 4 days The Rehfuss tubes swallowed were 7 feet in length and eventually (on the fourth day) reached about the midportion of the jejunum Twelve samples were removed from 1½ to 3 hours after ordinary meals The average acidity was pH 5 2 with a maximum of pH 4 1 and a minimum of pH 6 5 Measurements made on the fourth and fifth days, i e , after the tubes had nearly reached the maximum depth, averaged somewhat higher (pH 5 4) than those made on the first two days (pH 4 8) All measurements were made electrometrically and loss of CO_2 was prevented From the above data it seems logical to assume that normally the contents of the small intestine, at least as far as the midportion of the jejunum, are decidedly on the acid side of neutrality—a reaction unfavorable to the formation of *B Welchii* spores

The chief contribution to the acidity of the upper intestinal contents must be the gastric juice, which normally is usually considered equivalent to 1500 cc. of N/10 HCl per day The pancreatic juice is strongly alkaline, the intestinal juice somewhat less alkaline, and bile slightly alkaline In conditions of achylia it is difficult to conceive of the reaction of the upper intestinal contents as being anything but alkaline In the normal gastro intestinal tract it seems probable that the gastric juice and the acid by products of digestion

are sufficient to keep the reaction of the intestinal contents on the acid side of neutrality as far as the lower ileum, and possibly the cecum. The reaction is such that spore formation can not occur to any marked degree until the colon is reached. In conditions of achylia, however, spores may be formed not only in the large intestine, but also in the small intestine.

The importance of the normal secretion of gastric juice in determining the flora of the small intestine has been recently emphasized by Bogendorfer (23) and by Arnold and Brody (24). The former was able to recover *B. coli* and *B. Welchii* from the contents of the upper small intestine (tube length 2.0–2.5 meters) in cases of anacidity and gastric achylia including 2 cases of pernicious anemia, whereas those organisms were never found in cases with normal gastric secretion. The latter have reported a series of experiments on dogs in which the bacterial flora of the duodenum and upper jejunum has been shifted to resemble that of the ileum and colon by changing the normal reaction (pH 5.0–6.0) to neutral or slightly alkaline (pH 7.0–8.0). Van der Reis (6) (25) has demonstrated that a similar shift of flora occurs in cases of pernicious anemia. In addition to *B. coli* in the upper portions of the small intestine, he was able to recover sporulating anaerobic bacilli from the middle and lower portions—results not obtainable in cases without achylia.

It seems probable that *B. Welchii* is not a normal inhabitant of the upper small intestine. In the presence of achylia, however, this organism, together with others, notably *B. coli*, characteristic of the flora of the colon, work their way upwards and may be recovered even as high as the duodenum. It is not surprising that a marked increase in *B. Welchii* spore formation should occur. One would expect an increase in vegetative forms, but curiously such an increase can not be demonstrated, at least by the method of stained smear preparations of the feces.

Several other facts and observations tend to oppose the hypothesis that *B. Welchii* is the etiological factor in pernicious anemia. In the first place, the severe diarrheas accompanied by, possibly due to, a marked increase of *B. Welchii* in the intestinal contents do not result in any noteworthy anemia. Secondly, the experimental anemias brought about by Kahn and Torrey (11) are very acute in character,

identical with those brought about by the intravenous injections of any powerfully hemolytic agent, and, furthermore, there is marked reaction by the animal in the production of antihemolysin Thirdly, Tenbroeck and Bauer (26) have demonstrated appreciable amounts of tetanus antitoxin in the serums from human beings harboring spores of *B tetanus* in their gastro-intestinal tracts and from guinea pigs which have been fed large amounts of tetanus spores, and they remark that in the latter, although the tetanus bacillus is known to produce powerful hemolysins, no ill effects were noted If pernicious anemia were due to continued absorption of *B Welchii* toxin from the gastro intestinal tract one would expect to find the tissue cells active in antitoxin production Failure in certain individuals to produce antitoxin, either because of inherent inability or pos sibly toxin hypersusceptibility, might result in the development of severe anemias In such an instance one would expect to find a relatively low concentration of *B Welchii* antihemolysins in the serum, and probably a marked reaction following intradermal injection of *B Welchii* toxin Preliminary experiments indicate that the toxin neutralizing properties of the serums and the skin reactions of individuals suffering from pernicious anemia are essentially identical with those of normal individuals These investigations have not been carried out in sufficient detail to warrant inclusion in the present paper

The abnormal flora of the small intestine, secondary to the gastric achylia, may very possibly result in changes in the gastro intestinal tract which eventually lead to the disease, pernicious anemia Weinberg (27) believes that true achylia gastrica (not achylia secondary to chronic gastritis) is an hereditary condition, and that the individuals born with achylia gastrica are the ones in whom pernicious anemia may eventually develop Many other investigators, however, are opposed to the idea, and it does seem quite unusual that the development of pernicious anemia should be deferred so many years

CONCLUSIONS

1 In stools from cases of pernicious anemia there is a great increase in the number of *B Welchii* spores as compared with normal stools and stools from the majority of cases of miscellaneous disease

2 This same increase in *B Welchii* spores is also present in stools from cases of gastric achylia without pernicious anemia

3 Counts of vegetative forms would seem to indicate that in any of the above conditions the number of active or vegetative forms of *B Welchii* present in the stools are practically the same

4 On the basis of the above observations and the tendency of *B Welchii* to form spores in alkaline media, it seems logical to assume that the spore increase in pernicious anemia is secondary to the gastric achylia rather than indicative that pernicious anemia is caused by chronic intestinal infection with *B Welchii*

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STUDIES UPON OBESITY THE SOURCE OF HEAT DURING PERIODS OF REDUCTION

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The term antiketogenesis was introduced into the American from the German literature by Woodyatt (1) when reporting experimental studies with glycol aldehyd and glycerin aldehyd in a limited number of cases of severe diabetes mellitus He suggested that as the basis of antiketogenesis there was a little understood reaction between one molecule of acetoacetic acid and one molecule of glucose or alcohol Later Woodyatt (2) discussed Zeller's experiments on the feeding of iso-caloric low protein diets and Lusk's views on the fatty acid glucose molecular ratio The latter concluded that, omitting protein metabolism, six molecules of higher fatty acid required at least two molecules of glucose for its complete oxidation Lusk (3) in re-calculating Zeller's experiments, suggested that one triose molecule might be sufficient for the complete oxidation of one molecule of a higher fatty acid

Shaffer (4) in 1920 reported a series of in vitro experiments, based upon the oxidation of acetoacetic acid by hydrogen peroxide in the presence of glucose, from which he concluded that one molecule of glucose is necessary for the complete oxidation of one molecule of acetoacetic acid Woodyatt (5), working with diabetic patients under standard conditions in which he was able to determine the foodstuffs actually catabolized with a considerable degree of accuracy, concluded that the ratio as then stated by Shaffer was in accordance with his results

That the molecular ratio of 1 1 might be too low was indicated by the work of Wilder and Winter (6) who investigated the threshold of ketogenesis in sixteen patients, thirteen diabetics and three cases of epilepsy They concluded that "the ratio between the ketogenic and

glucose molecules at which a clinically significant ketosis appears has a value of at least 2 1 " The probability of this higher ratio was subsequently supported by Shaffer (7) based upon in vitro experiments and calculations of the expected excess of ketogenic molecules in cases of marked ketosis Employing his earlier molecular ratio of 1 1 Shaffer found that in the presence of marked ketosis the acetone bodies actually found were considerably in excess of that predicted by calculation This fact he believed indicated an error in the earlier ratio which was supported by later in vitro experiments indicative that one molecule of glucose is capable of oxidizing two molecules of keto-acid when the latter is present in excess Applying a ratio of 1 2 calculations on suitable cases from the literature predicted less acetone than was actually found In order to correct this discrepancy Shaffer suggested that protein yielded more ketogenic material than formerly estimated By increasing the ketogenic factor from protein by 50 per cent his calculations showed much better agreement

More recently Harding and Allin (8) have reported a series of experiments to determine the threshold of ketonuria in normal pregnant women Employing the factors used by Shaffer (4) in his first ratio they found that on the whole the molecular ratio of 1 to 1 held in pregnancy the same as in the non-pregnant condition Nevertheless it was noted that ratios up to 1 1 47 resulted in no greatly increased excretion of acetone bodies

EXPERIMENTAL STUDIES

In the study of a series of cases of obesity undergoing reduction through the means of a sub-caloric diet, it became evident that an extreme percentage of their calories were being derived from their body fat, and that this was taking place without any ketosis developing after the first ten days of the restricted diet

In this communication are recorded the data upon five such cases of so-called "exogenous" obesity maintained continuously in the hospital for a prolonged period of time upon a sub-caloric diet They were not confined to bed, but exercised daily, and three times per week were given hydrotherapy treatments In no case after the tenth day of the sub-caloric diet was there any evidence of ketosis as determined by daily urinary ferric chloride tests, and frequent plasma CO_2 capac-

ity determinations In the tabulation of the data it was found to be convenient to record it in consecutive ten day periods as will be seen in the subsequent tables

ANALYTICAL METHODS

All urines were collected in 24-hour periods and preserved under toluol Total nitrogen was determined by the Kjeldahl-Gunning method CO_2 capacities on the blood plasma were done according to Van Slyke's technique

CALCULATION OF RESULTS

Data were obtained which enabled one to calculate with a considerable degree of exactness the mixtures of foodstuffs oxidizing in their bodies

1 Total metabolism The total calories produced were assumed to be 20 per cent greater than the level of the basal metabolism This estimate was considered to be very conservative in view of the fact that all the patients were dressed and active throughout the day, and were given hydrotherapy three times each week Since the basal metabolic rate was determined at least twice each week an accurate calculation could be made of the average basal heat production in ten day periods

2 Protein combustion The protein oxidized was calculated from the urinary nitrogen which was actually determined, adding 5 per cent for the stool nitrogen The assumption that only 5 per cent of the total nitrogen excreted was lost by the stool was considered to be justified in view of the very low diets The factor 26 51 was used for converted grams of nitrogen into protein calories

3 Carbohydrate combustion Since the first five to ten days of the low diets were excluded the assumption that the glycogen deposits were appreciably reduced was made, and the carbohydrate oxidized calculated as being derived only from the intake The food carbohydrate was figured from Atwater and Byrant's average values, each gram being estimated to yield 4 1 calories

4 Fat combustion The calories derived from fat were calculated as the difference between the total calories produced and the sum

of the protein and carbohydrate calories The fat calories were converted into grams of fat oxidized by the factor 9 3, which factor was considered to be most suitable since the major part of the fat oxidized came from the patient's own tissues

5 *The ketogenic antiketogenic ratio* The calculation of the ketogenic antiketogenic ratio was made upon the first set of values as given by Shaffer (4), in which the assumption was made that one molecule of glucose is antiketogenic for one molecule of acetoacetic acid

	Ketogenic	Antiketogenic
	mM	*mM*
1 gram fat	3 43	0 57
1 gram glucose	0 00	5 56
1 gram N (Urine plus stool)	10 00	20 00

TABLE 1

Loss of weight during reduction

Case	Sex	Age	Weight		Total loss	Total loss	Days	Loss per day
			Admission	Discharge				
		years	*kgm*	*kgm*	*kgm*	*pounds*		*kgm*
I (El)	F	36	112 5	92 4	20 1	44 2	63	0 318
II (Ro)	F	51	172 9	138 2	34 7	76 3	90	0 386
III (Ho)	F	50	149 1	124 8	24 3	53 5	64	0 380
IV (Ki)	F	31	123 6	87 5	36 1	79 4	108	0 334
V (Kr)	F	29	109 9	78 6	31 3	68 9	117	0 268

Loss of weight during reduction As seen in table 1, the total loss of weight varied from 20 1 to 36 1 kgm The loss per day paralleled the initial weight directly, being greatest with the largest initial weight

Food intake during reduction The diet administered to each case during the experimental periods of ten days each is shown in table 2 In cases II and III the first ten days, in cases I and V the first nine days, and in case IV the first five days of the sub-caloric diets have been excluded In all cases the type of diet during the periods excluded was the same as that during the first accepted ten day periods

TABLE 2

Food intake during periods of reduction

Periods	Case I (El)			Case II (Ro)			Case III (Ho)			Case IV (Kl)			Case V (Kr)		
	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate	Protein	Fat	Carbohydrate
(10 days each)	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
1	395	49	100	236	105	104	550	200	625	493	154	250	495	152	250
2	400	50	100	254	81	132	490	188	465	331	91	165	449	138	350
3	400	50	100	253	68	197	400	80	150	370	112	215	415	117	469
4	427	48	97	253	69	202	400	80	150	329	98	325	178	44	396
5	453	71	148	246	65	194	430	104	210	114	42	600	137	38	413
6	150	48	108	187	58	159				134	45	602	74	22	359
7	(Last period 3 days)			265	69	145				323	102	639	117	39	353
8										130	35	600	92	30	282
9										293	123	500	143	50	347
10										186	68	360	45	14	280
										(Last period 7 days)					

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TABLE 3

Nitrogen balance during periods of reduction

Period	Case I (El)			Case II (Ro)			Case III (Ho)			Case IV (Ki)			Case V (Kr)		
	Intake	Output	Balance	Intake	Output	Balance	Intake	Output	Balance	Intake	Output	Balance	Intake	Output	Balance
(10 days each)	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
1	63 1	127 6	−64 5	37 6	94 9	−57 3	88 0	116 7	−28 7	78 9	133 0	−54 1	79 0	117 4	−38 4
2	64 0	100 3	−36 3	40 6	81 4	−40 8	78 4	125 6	−47 2	53 0	109 5	−56 5	71 6	74 6	−3 0
3	64 0	64 0	+0	40 5	78 6	−38 1	64 0	112 5	−48 5	59 1	81 9	−22 8	66 4	76 3	−9 9
4	68 4	67 6	+0 8	40 4	67 5	−27 1	64 0	85 8	−21 8	52 5	66 1	−13 6	28 4	57 9	−29 5
5	72 5	65 7	+6 8	39 2	51 7	−12 5	68 8	82 6	−13 8	18 2	59 0	−40 8	21 9	50 1	−28 2
6	24 0	18 4	+5 6	30 0	50 9	−20 9				21 5	51 0	−29 5	11 8	41 4	−29 6
7	(Last period 3 days)			42 4	62 4	−20 0				51 6	55 6	−4 0	18 8	40 1	−21 3
8										20 8	44 0	−23 2	14 6	34 3	−19 7
9										47 0	56 8	−9 8	22 8	47 1	−24 3
10										29 8	35 4	−5 6	7 3	34 6	−27 3
										(Last period 7 days)					
	Total N loss to body (63 days) = 87 6 grams Per day = 1 39 grams			(70 days) = 216 7 grams Per day = 3 10 grams			(50 days) = 160 0 grams Per day = 3 20 grams			97 days) = 259 9 grams Per day = 2 68 grams			(100 days) = 231 2 grams Per day = 2 31 grams		

Its extreme sub-caloric nature and duration would tend to add accuracy to the calculations and especially to the assumption that the glycogen deposits were largely exhausted

Nitrogen balance during reduction The total nitrogen loss to the body varied from 1 39 to 3 20 grams per day as shown in table 3 In case I a slightly positive nitrogen balance was maintained during the last thirteen days of the experimental period This was associated with a falling basal metabolic rate, the average basal production of calories in the six consecutive periods being, 1694, 1597, 1582, 1537,

TABLE 4

Source of heat during periods of reduction

Period 10 days each	Percentage of total calories (basal plus 20 per cent) from														
	Protein					Fat					Carbohydrate				
	Case I	Case II	Case III	Case IV	Case V	Case I	Case II	Case III	Case IV	Case V	Case I	Case II	Case III	Case IV	Case V
1	16 6	9 4	11 8	13 4	13 6	81 4	89 0	78 4	82 7	81 9	2 0	1 6	9 8	3 9	4 5
2	13 9	8 0	12 7	11 8	8 8	84 0	90 0	80 0	85 4	84 8	2 1	2 0	7 3	2 8	6 4
3	8 9	7 4	11 4	9 0	9 0	88 9	89 7	86 2	87 4	82 5	2 2	2 9	2 4	3 6	8 5
4	9 7	6 5	9 3	7 0	6 7	88 1	90 5	88 2	87 7	85 3	2 2	3 0	2 5	5 3	7 0
5	9 8	5 6	8 7	6 3	6 0	86 8	91 2	87 9	83 7	86 3	3 4	3 2	3 4	10 0	7 7
6	8 7	5 4		5 6	5 2	83 7	92 0		84 1	87 8	7 6	2 6		10 3	7 0
7		6 3		6 3	5 2		91 4		82 6	87 7		2 3		11 1	7 1
8				5 1	4 7				84 2	89 4				10 7	5 9
9				6 6	6 6				84 5	85 9				8 9	7 5
10				5 9	4 9				84 9	88 9				9 2	6 2
Average	11 3	6 9	10 8	7 7	7 1	85 5	90 1	84 3	84 7	86 1	3 2	2 5	5 1	7 6	6 8

1478, and 1552 That the patient was able to maintain a state of nitrogen equilibrium during the last thirty-three days of the sub-caloric diet is very unusual There is some relationship between the loss of body nitrogen per day and the total loss of weight per day In those cases losing weight more rapidly there was a greater loss per day of body nitrogen

Source of heat during reduction The percentage of total calories derived from protein, fat and carbohydrate is shown in table 4 This percentage is based upon the assumed total metabolism which

TABLE 5

Ketogenic-antiketogenic balance

Case	Period 10 days each	Total N urine plus stool	Oxidized		Ketogenic K'	Antiketogenic A'	Ratio $\frac{K}{A}$	Remarks
			Fat	Carbohydrate				
		grams	*grams*	*grams*	*mM*	*mM*		
I (El)	1	127 6	1,778	100	7,375	4,120	1 79	First nine days of con-
	2	100 3	1,730	100	6,937	3,549	1 95	trolled low diet ex-
	3	64 0	1,812	100	6,855	2,871	2 39	cluded Period no 6
	4	67 6	1,748	97	6,672	2,890	2 31	three days only
	5	65 7	1,652	148	6,323	3,081	2 05	
	6	18 4	503	108	1,909	1,255	1 52	
II (Ro)	1	94 9	2,560	104	9,730	3,935	2 48	First ten days of con-
	2	81 4	2,607	132	9,756	3,847	2 54	trolled low diet
	3	78 6	2,702	197	10,053	4,206	2 38	excluded
	4	67 5	2,717	202	9,994	4,020	2 48	
	5	51 7	2,400	194	8,749	3,474	2 52	
	6	50 9	2,480	159	9,015	3,313	2 72	
	7	62 4	2,583	145	9,484	3,530	2 68	
III (Ho)	1	116 7	2,199	625	8,709	7,064	1 26	First ten days of con-
	2	125 6	2,253	465	8,984	6,381	1 41	trolled low diet ex-
	3	112 5	2,421	150	9,429	4,465	2 10	cluded
	4	85 8	2,330	150	8,850	3,881	2 28	
	5	82 6	2,378	210	8,972	4,176	2 15	
IV (Ki)	1	133 0	2,340	250	9,356	5,385	1 74	First five days of con-
	2	109 5	2,260	165	8,847	4,398	2 01	trolled low diet ex-
	3	81 9	2,272	215	8,612	4,130	2 08	cluded
	4	66 1	2,360	325	8,756	4,478	1 96	
	5	59 0	2,220	600	8,205	5,786	1 42	
	6	51 0	2,161	602	7,922	5,598	1 42	
	7	55 6	2,082	639	7,697	5,852	1 31	
	8	44 0	2,080	600	7,574	5,408	1 40	
	9	56 8	2,075	500	7,685	5,078	1 51	Period no 10 seven
	10	35 4	1,458	360	5,354	3,541	1 51	days only
V (Kr)	1	117 4	2,004	250	8,048	4,883	1 65	First nine days of con-
	2	74 6	2,047	350	7,767	4,608	1 68	trolled low diet ex-
	3	76 3	1,997	469	7,603	5,266	1 41	cluded
	4	57 9	2,137	396	7,909	4,593	1 72	
	5	50 1	2,046	413	7,518	4,466	1 68	
	6	41 4	1,990	359	7,240	3,962	1 83	
	7	40 1	1,916	353	6,972	3,856	1 81	
	8	34 3	1,879	282	6,788	3,329	2 04	
	9	47 1	1,740	347	6,439	3,866	1 66	
	10	34 6	1,772	280	5,424	3,261	1 66	

has been estimated to be 20 per cent greater than the basal metabolism. In three of the five cases protein averaged to supply less than 10 per cent of the total calories. The greatest average was 11.3 and the smallest 6.9 per cent. In all cases more than 80 per cent of the total calories were derived from fat, the average in case II being 90.1 per cent. Carbohydrate averaged to supply from 2.5 to 7.6 per cent of the total calories.

Ketogenic-antiketogenic balance. The ketogenic antiketogenic balance is tabulated in table 5. The factors are expressed in millimols employing the values as stated by Shaffer (4) when based upon the assumption that one molecule of glucose is antiketogenic for one molecule of acetoacetic acid. The constancy of the ratios in consecutive ten day periods speaks strongly for the justification of the assumption that little glycogen was available in the body at the beginning of the accepted experimental periods.

In all cases the ratio of the ketogenic to the antiketogenic molecules exceeds 1:1. In case II, the same ratio consistently exceeds 1:2, and it should be noted that the experimental periods extended over seventy consecutive days. In all cases during these accepted experimental periods there was no detectable ketosis.

DISCUSSION

The above data are difficult to coördinate with the present conception of the ketogenic antiketogenic balance. The findings in case II alone, where for seventy consecutive days a molecular ratio exceeding 1:2, Shaffer's (7) latest in vitro analogy, was oxidized without ketosis, reopens the question of the accuracy of the fundamental conception of the ketogenic antiketogenic balance. Shaffer's (7) idea, based upon expected calculations only, that the ketogenic molecules from protein were underestimated by fifty per cent would make the reported ratios still higher.

That the human body has the capacity for adaptation has been suggested by Joslin (9) and he further has stated that there is most likely an essential difference between the ketonuria of the diabetic and the non-diabetic individual. Folin and Denis (10) in studies upon two obese women during successive fasts, also came to the conclusion that the human organism is capable of adaptation. They

noted that with repeated fasting periods habituation to the complete oxidation of mobilized body fat followed Considered from the viewpoint of comparative physiology it was a contributing observation that the dog and rat are very resistant to a fasting ketosis (Levine and Smith (11), Wigglesworth (12)) Baer (13) has reported a ketonuria with fasting in the monkey, but Harding and Allin (8) failed to produce ketonuria in a Dalmatian dog excreting uric acid either by fasting or by diets high in fat The susceptibilities of puppies to ketosis, clearly shown by Allen (14), while the adult dog is very resistant, Harding (8) states may be "an expression of the non-development of the physiological regulatory mechanism until adult life "

The possibility that glucose exerts its ketolytic action as a triose was first recognized by Lusk (3) but still remains unproven

In recent years more and more evidence has been accumulating to the effect that the normal and the diabetic individual may be able to convert fat into carbohydrate Lawrence (15) has recently called attention to the evidence that by far the greater percentage of one's total metabolism, both in the active and resting state, is due to muscular activity, and that in muscular activity carbohydrate is the only substance known to be burned This was shown by Krogh and Lindhard (16) through respiratory quotient studies, and has been confirmed by Furusawa (17) in a study of the rate of fall of the respiratory quotient after exercise Similar data has been presented by Hetzel and Long (18) working with the diabetic individual with a lowered glycogen reserve Finally, Burn and Marks (19) have published well controlled experiments which show that the perfusion of a liver removed from the body with defibrinated blood at 37°C results in the production of sugar in the perfusing fluid to an extent greater than can be accounted for by the disappearance of glycogen alone The rate of sugar formation amounted to 2 to 4 mgm per gram of liver per hour, and could be maintained at that rate for three hours provided a small amount of adrenalin be added to the perfusion fluid Similar results were obtained using livers rendered almost carbohydrate free by feeding the animals with fat diets The possibility of this excess sugar coming from lactic acid was excluded Nitrogen studies controlled the amount derivable from protein

SUMMARY

Studies upon five cases of obesity maintained upon sub-caloric diets for prolonged periods of time are reported Sufficient data were obtained to enable one to estimate with a fair degree of accuracy the mixture of foodstuffs actually catabolizing in the body

In all cases the ketogenic-antiketogenic molecular ratio exceeded 1 1 In one case, No II, the same ratio exceeded 1 2 throughout an experimental period of seventy consecutive days In no case, during the experimental periods, was there any evidence of ketosis

A discussion is presented of some of the various possibilities for an explanation of the above findings

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OXY-HEMOGLOBIN DISSOCIATION CURVES OF WHOLE BLOOD IN ANEMIA

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Although the oxy-hemoglobin dissociation curves of normal whole blood have been extensively studied for many years (1, 2, 3), there has been relatively little investigation of these curves in the blood of abnormal subjects

Meakins, Dautrebande and Fetter (4), in their work on circulatory stasis in 1923, published some oxygen dissociation curves of patients with cardiac decompensation, showing that at or near 40 mm CO_2 tension, these curves did not deviate appreciably from those of normal blood Stadie and Martin (5), investigating carbon monoxide hemoglobin and oxy-hemoglobin relations, included one oxygen dissociation curve of a patient with pernicious anemia This was at 40 mm CO_2 tension, and was an apparently normal curve Odaira (6) stated that in severe anemia the oxygen curves were lowered, but did not state at what CO_2 tension or serum pH these curves were determined

The present investigation represents a study of the oxy-hemoglobin dissociation curves of the whole blood of several subjects with anemia from various causes, and of one with advanced polycythemia vera It comprises the following (*a*) at serum pH (or pH_s) 7 44 (CO_2 tension approximately 40 mm), points on the O_2 dissociation curves of five primary anemias, two secondary anemias, and one polycythemia vera, (*b*) at pH_s 7 64 (CO_2 tension approximately 20 mm), points on the curves of three primary and two secondary anemias, (*c*) at pH_s 7 24 (CO_2 tension approximately 80 mm), points on the curves of one primary and one secondary anemia A control curve of the blood of one of us was also done at each of these CO_2 tensions

METHODS

Blood was drawn from an arm vein, with stasis of one minute or less, into a container with enough neutralized dried potassium oxalate, and dried sodium fluoride to make a concentration of approximately 0 2 per cent of the former and 0 1 per cent of the latter Tonometers of 300 cc capacity were filled with the desired CO_2 and O_2 mixtures by the manometer method outlined by Van Slyke, Wu and McLean (7) Five cubic centimeters of blood were introduced into each tonometer Two tonometers were then put into a water bath at 38, ± 0 2°C, and rotated for forty minutes or more The other tonometers were put in the ice box, and equilibrated later The gases in the equilibrating tonometers were brought to atmospheric pressure at 38°, by allowing excess gas to escape at the beginning of the equilibration and again after about ten minutes of rotating The effect of equilibrating the blood in the tonometers for longer than forty minutes was tested on the blood of one of us (see table 1, experiment of March 29th) at an oxygen tension of 20 mm There was no measurable change in the oxygen capacity of the blood in the tonometers after either two hours' or four hours' rotation After equilibration the blood was withdrawn directly into 1 cc stopcock-pipettes, and then transferred for oxygen or CO_2 determination to a Van Slyke-Neill constant volume apparatus Samples of the tonometer gases were collected in gas sampling tubes and their CO_2 and O_2 contents determined later by the Haldane gas analysis apparatus The above procedure is in general that of the "first saturation method" of Austin, Cullen *et al* (8)

In two of the earlier experiments, the blood was collected from the tonometers into test tubes under oil Under these conditions, however, the blood was found to absorb oxygen and lose CO_2, especially if stirring was necessary, as was usually the case on account of the rapid settling of anemic blood The transfer of blood directly to pipettes saved one step in manipulation, was easily accomplished by connecting three or four pipettes successively to the tonometer by a bent glass tube connection, and drawing the blood into them, and this method gave duplicate determinations that checked satisfactorily A pipette full of blood could be left standing several minutes without measurably changing the O_2 content

Oxygen capacity determinations were in most cases made after equilibrating the blood in air at room temperature, occasionally in tonometers at 38°C, the proper value for dissolved O_2 being applied in each case

There was considerably greater difficulty in obtaining an accurate curve from a markedly anemic blood than from normal blood This was partly because of the rapidity of settling of the red cells, and partly because of the magnification of errors in per cent oxygen saturation when the oxygen capacity was small In the first two of our primary anemia curves at 40 mm CO_2 tension, in which the blood after equilibration was collected under oil, our duplicate determinations did not check closely In the succeeding experiments, a total of 61 points on abnormal blood curves were determined duplicate determinations on two of them checked only to 0 4 volume per cent, four others to 0 3 volumes per cent, and

four points were based on a single oxygen content determination Duplicate measurements for the other points checked within the error of the method 0 2 volumes per cent Of 31 points on our control blood, three checked only to 0 4 volumes per cent, the rest within the error of the method An exception is made of the case of W B, (table 3), a secondary anemia whose major condition was myelogenous leukemia His white blood count was 700,000, and his blood was found to diminish rapidly in O_2 content on standing, so that we were compelled to use for our curve only the first oxygen measurement after equilibration of the blood the first pipetteful of blood being transferred as rapidly as possible from the tonometer to a Van Slyke apparatus containing air free ferricyanide solution

CORRECTIONS

The form of the dissociation curve of oxy-hemoglobin has been shown, by Adair (9) and others, to depend primarily on the pH of the solution, although the content of bicarbonate and other electrolytes also influences the levels of the curves to some extent (10, 11, 1) For the comparison of oxygen dissociation curves of the whole blood of different individuals, it would therefore probably be best to have all curves corrected to the same cell pH (or pH_c) Such corrections can be made, as fairly good approximations, by the use of the Donnan ratio r, as developed by Van Slyke, Wu and McLean (7), if the pH_s and percentage oxygen saturation are known When these corrections are worked out, however, using the data of Bock, Field and Adair (3), it is found that the differences between the curves at constant pH_c, at constant pH_s, and at constant CO_2 tension, are small, and although the larger corrections are outside the limits of the experimental error, they are smaller than the recognized and as yet unexplained differences between the blood of different normal individuals We have, therefore, in these curves simply determined the pH_s of the oxygenated blood at the desired CO_2 tension, 20, 40, or 80 mm, and if this pH_s value has differed by more than 0 04 from that of the standard normal curves, a correction has been applied to all the points on that curve Four of the curves, one primary anemia, two secondary anemias, and one control blood, required such a correction The corrections have been made in the O_2 tension by interpolation, using the curves of Bock, Field, and Adair as standards

The pH_s was determined gasometrically, by the Henderson-Hasselbalch formula The CO_2 content of the oxygenated blood at the

desired CO_2 tension was determined by measuring the CO_2 content (either whole blood or "true" serum) of the blood in the tonometer having the highest O_2 tension This blood was, in the various cases, from 90 to 98 per cent saturated with oxygen The CO_2 tension, as measured, varied usually a few millimeters from the exact value desired, i e , 20, 40, or 80 A small extrapolation on the CO_2 curve, with correction for oxygen unsaturation, then gave the CO_2 content of fully oxygenated blood at the exact CO_2 tension, with sufficient accuracy In some of the determinations we measured the whole blood CO_2 content and in others that of the "true" serum In the former case the pH_s was determined by the method outlined by Van Slyke, Wu and McLean (7), using their Δ pK′ values We used 6 13 as the pK′ value, and $\alpha_{CO_2} = 0\ 555$ per Kg of blood water for the solubility factor, as employed by Van Slyke, Hastings, Murray and Sendroy (12) These constants gave slightly different pH_s values to our curves, and also to the curves of Bock, Field, and Adair, than when computed by using the constants of Van Slyke's earlier paper (7)

In as much as in our gas equilibrations we used the "first saturation method" of Austin, Cullen, *et al* (8), the CO_2 tensions in the tonometers were only approximately correct and the Haldane analyses after equilibration frequently showed the final CO_2 tensions to be several millimeters from the desired tensions of 20, 40, or 80 mm A correction formula was developed on the basis of the empirical linear relation between CO_2 tension and 1/K of Hill's equation, a relation which L J Henderson (13) found to be approximately true when applied to Barcroft's blood curves, and which he expressed in the formula $\frac{p_{CO_2} + 7\ 7}{0\ 014} = \frac{Hb}{HbO_2}(pO_2)^{2\ 5}$ The correction formula which we have used is the same in principle as that used by Bock, Field and Adair, and is, for the 40 mm curves, as follows

$$\log p_{O_{2_{40}}} = \frac{1}{2\ 5}\log\left[(40 + 7\ 7) + 2\ 5\log p_{O_2} - \log(p_{CO_2} + 7\ 7)\right]$$

where $p_{O_{2_{40}}}$ = O_2 tension at 40 mm CO_2 tension

p_{O_2} = O_2 tension as measured

p_{CO_2} = CO_2 tension as measured

As a matter of fact, except in the cases of the larger corrections, especially those near 100 per cent oxygen saturation, little difference was found between the corrections, based on the above formula, and those found merely by interpolation, using as standards the curves of Bock, Field and Adair The method of interpolation, being simpler, was therefore usually employed for the smaller corrections

DISCUSSION

The data for all the curves are tabulated in tables 1, 2 and 3, and the points charted in figures 1 to 3 The drawn curves in the figures, included for purposes of comparison, are reproduced from the data of Bock, Field and Adair, the continuous lines being from the blood of A V B and the interrupted line from that of G S A Clinical data in regard to the patients studied are given in table 4

It will be seen that all the $pH_s = 7\ 44$ curves fall fairly close to the normal ones, both for primary and secondary anemias There is perhaps a tendency for the anemic curves to lie at a little lower level, especially in the upper part of their course, than the normals The polycythemia curve shows no evidence of abnormality

The points on the $pH_s = 7\ 24$ curves also are fairly close to each other, the normal curve here, however, does not agree as well with that of A V B We have no special comment to offer on this latter point, except that for some reason a smooth and accurate curve is, in general, more difficult to obtain at this high CO_2 tension Bock, Field, and Adair encountered the same thing in their work. In our final normal control experiment, all oxygen determinations were done in triplicate, and the average of the closest two values were taken for each point

At the more alkaline reaction of $pH_s = 7\ 64$ there are obviously distinct differences between the curves of the individuals studied The number of curves is, of course, small, and it is therefore quite possible that the variations in the levels of the curves simply represent variations that might occur between the oxygen dissociation curves of any small group of normal individuals That such differences do occur has been known since Barcroft's early work (1) It is clear from an examination of figure 2, however, that our normal control curve is close to that of A V B , and that the anemia curves

TABLE 1

Subject	Condition	Date	CO_2 tension	O_2 tension	Total O_2	HbO_2	p_{O_2} (at P_{CO_2} = 40 mm)	p_{O_2} (at pH_s = 7 44)	
			mm	*mm*	*vols per cent*	*per cent*	*mm*	*mm*	
D W R Male 30	Normal subject	April 30	46 0	136 0	21 5	100 0	—		Total CO_2, oxygenated blood (at P_{CO_2} = 40 mm) = 49 1 vols per cent, pH_s = 7 46 Cell volume = 45 per cent $\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}}$ = 0 47
		March 1	air	air	22 3	100 0	—		
			39 7	15 3	4 7	21 6	15 3		
			36 1	22 7	9 7	44 0	23 7		
			37 6	62 8	20 6	93 5	65 0		
			38 0	73 7	21 2	96 3	75 9		
			35 9	33 4	14 6	66 5	34 4		
			39 8	42 1	17 2	78 3	42 1		
		March 16	42 2	52 7	19 5	89 0	52 2		
			42 9	87 8	21 4	97 3	86 5		
			44 3	4 0	1 5	6 9	4 0		
			41 3	7 6	1 8	8 2	7 6		
			air	air	22 3	100 0	—		
		March 29	air	air	22 8	100 0	—		
			44 0	25 6	10 2	45 2	24 9		
			air	air	22 9	100 0	—		
			43 6	24 1	10 0	44 1	23 5		
			air	air	22 8	100 0	—		
			43 6	24 3	10 0	44 4	23 5		

M C. Male, 62	Pernicious anemia	March 9	44 4	38 7	7 9	68 5	37 7	34 1	Total CO_2 oxygenated blood (true serum) (at p_{CO_2} = 40 mm.) = 49 0 vols. per cent, pH_s = 7 36
			44 4	6 7	0 9	7 9	7 8	6 6	
			44 0	58 2	10 2	88 5	57 2	52 8	
			44 2	18 6	2 9	25 9	18 0	15 8	
			44 6	75 8	10 8	93 0	74 5	70 1	
			59 4	70 9	—	—	—	—	
			air	air	11 9	100 0	—	—	
H. Sa. Male 39	Pernicious anemia	February 26	air	air	16 9	100 0	—		
			40 6	11 9	2 8	17 1	11 9		
			39 6	29 3	9 2	55 5	29 3		
			23 2	39 0	13 9	84 0	48 0		
H. St. Female 49	Pernicious anemia	March 20	air	air	8 8	100 0	—		Total CO_2, oxygenated blood (at p_{CO_2} = 40 mm.) = 53.5 vols per cent, pH_s = 7 43 Cell volume = 14 per cent $\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}} = 0\ 59$
			38 1	59 7	7 7	90 4	61 0		
			37 1	24 2	3 6	42 8	24 7		
C. G Female 67	Pernicious anemia	March 26	air	air	8 7	100 0	—		pH_s = 7 44 (March 26), 7 46 (April 2), 7 46 (April 9) Cell volume (March 26) 14.5 per cent $\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}} = 0.57$
			40 7	60 2	7 7	91 4	60 0		
			40 5	51 3	7 1	85 3	51 2		
			38 6	31 4	4 9	58 5	31 8		
			39 9	23 8	3 2	38 5	23 8		
		April 2	air	air	14 1	100 0	—		
			36 6	72 1	13 2	95 5	75 7		
			37 6	42 8	10 5	76 3	43 8		
		April 9	air	air	13 5	100 0	—		
			42 4	11 5	2 7	20 6	11 2		
			32 1	82 3	12 7	96 2	89 2		
			42 4	21 8	5 1	38 8	21 4		

TABLE 1—*Continued*

Subject	Condition	Date	CO_2 tension	O_2 tension	Total O_2	HbO_2	p_{O_2} (at p_{CO_2} = 40 mm.)	p_{O_2} (at pH_s = 7 44)	
			mm	*mm*	*vols per cent*	*per cent*	*mm.*	*mm*	
M J Female 52	Polycythemia vera	April 16	air	air	27 4	100 0	—		Total CO_2, oxygenated blood (at p_{CO_2} = 40 mm.) = 46 6 vols per cent, pH_s = 7 48
			43 0	71 6	25 3	93 2	70 8		Cell volume = 62 per cent
			32 7	26 0	14 2	52 4	27 8		$\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}}$ = 0 43
			39 6	13 8	5 1	19 0	13 8		
			40 4	47 0	22 5	83 2	47 0		
V S Female 41	Secondary anemia	April 23	air	air	8 5	100 0	—		Total CO_2, oxygenated blood (at p_{CO_2} = 40 mm) = 60 0 vols per cent, pH_s = 7 48
			38 6	52 5	7 2	88 7	53 6		Cell volume not done
			46 3	65 3	7 5	91 3	61 7		
		April 22	43 3	10 1	1 3	16 2	9 8		
			38 7	30 2	4 7	57 5	30 6		
			41 7	69 3	7 9	96 2	68 5		
A. O Female 38	Pernicious anemia	March 17	24 9	150 0	4 6	100 0	—		pH_s = 7 46 (March 17), 7 43 (March 26)
			36 8	24 2	2 3	51 6	25 0		Cell volume (March 17) = 5 5 vols per cent
			37 4	45 5	3 6	83 3	46 8		
			32 5	71 6	4 2	95 0	76 3		

		March 27	air	air	6 8	100 0	—		$\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}} = 0\ 73$
			40 7	58 2	6 0	92 0	58 2		
			40 9	34 9	4 5	69 9	34 9		
			42 8	15 6	1 5	23 8	15 3		
			34 6	80 4	6 3	97 0	84 5		
			39 7	41 5	5 0	77 9	41 5		
P L.	Chronic nephritis,	May 5	air	air	16 9	100 0	—	—	Total CO_2, oxygenated blood (at
Male	secondary		39 2	20 4	6 0	36 6	20 6	22 0	P_{CO_2} = 40 mm.) = 70.5 vols.
58	anemia		40 6	42 3	13 7	82 9	42 1	46 3	per cent, pH_s = 7.52
			39 7	11 5	2 3	14 0	11 5	12 3	Cell volume = 35 per cent
			41 0	76 2	15 8	95 1	75 8	84 2	$\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}} = 0\ 47$
			36 0	29 9	10 5	63 4	31 1	34 1	
			39 3	57 3	15 2	92 0	57 8	65 0	

TABLE 2

Subject	Condition	Date	CO_2 tension	O_2 tension	Total O_2	HbO_2	p_{O_2} (at P_{CO_2} = 20 mm)	p_{O_2} (at pH_s = 7 64)	
			mm	*mm*	*vols per cent*	*per cent*	*mm*	*mm*	
D W R Male 30	Normal subject	April 30	22 0	15 9	6 7	31 6	15 5		pH_s (April 30) = 7 67 pH_s ("diluted blood") (at p_{CO_2} = 27 5) = 7 59
			22 8	37 7	17 3	81 2	36 3		Cell volume (April 30) = 45 per cent
			25 2	65 2	20 7	96 3	59 5		$\frac{O_2 \text{ capacity}}{\text{Cell vol per cent}} = 0\ 47$
			46 0	136 0	21 5	100 0	—		Cell volume ("diluted blood") = 28 per cent
		May 22	23 4	46 3	19 0	89 0	43 2		$\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}} = 0\ 48$
			20 3	11 8	3 9	18 1	11 8		
			22 2	23 5	11 9	55 4	22 9		
			air	air	21 8	100 0			
	"Diluted blood"	June 3	26 3	35 5	10 8	79 1	36 0	33 7	
			28 6	72 7	13 5	98 0	71 7	66 7	
			27 7	20 7	6 2	45 4	20 7	19 4	
			27 9	9 3	2 1	15 6	9 3	9 0	
			air	air	14 1	100 0	—		
H Sm Female 78	Pernicious anemia	May 17	air	air	12 4	100 0	—		Total CO_2, oxygenated blood (true serum) (at P_{CO_2} = 20 mm) = 42 5 vols per cent, pH_s = 7 60
			23 5	28 7	7 4	61 3	27 6		Cell volume = 23 per cent
			23 9	67 8	11 4	95 0	63 7		$\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}} = 0\ 52$
			29 1	11 6	1 9	16 0	10 7		
			23 6	49 3	10 6	87 9	47 0		
			21 7	19 0	4 7	39 5	18 7		

A. O	Pernicious anemia	May 25	air	air	8 8	100 0	—		Total CO_2 oxygenated blood (at
Female			23 0	21 1	3 4	38 0	20 5		p_{CO_2} = 20 mm.) = 45.5 vols.
38			23 7	51 8	8 0	88 5	49 4		per cent, pH_s = 7 68
			22 6	35 8	6 8	76 0	34 8		
H. St.	Pernicious anemia	May 27	air	air	9 9	100 0	—		Total CO_2 oxygenated blood (at
Female			17 6	76 9	9 2	95 7	78 5		p_{CO_2} = 20 mm.) = 39 0 vols.
49			21 1	11 4	1 3	13 9	11 4		per cent pH_s = 7 61
			23 8	20 2	3 2	33 7	19 0		Cell volume = *19* per cent
			16 0	36 6	7 7	80 5	38 8		$\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}}$ = 0.50
			24 0	61 7	8 9	92 5	57 5		
M. S	Bacterial endocarditis, secondary anemia	June 9	air	air	8 7	100 0	—		Total CO_2 oxygenated blood (at
Male			20 0	20 2	3 7	44 3	20 0	21 5	p_{CO_2} = 20 mm.) = 48.5 vols
29			25 2	33 2	6 2	73 8	30 7	33 0	per cent, pH_s = 7 70
			20 1	10 6	1 5	18 2	10 6	11 2	
			18 9	71 9	8 1	96 4	73 0	79 0	
V G	Secondary anemia	June 30	air	air	10 2	100 0	—		Total CO_2 oxygenated blood (at
Female			21 5	22 1	4 4	44 3	21 7		p_{CO_2} = 20 mm) = 40 8 vols.
31			24 1	36 5	7 3	74 2	34 9		per cent, pH_s = 7 65
			22 3	67 5	Lost	—	—		Cell volume = 22.5 per cent
									$\frac{\text{Oxygen capacity}}{\text{Cell vol. per cent}}$ = 0 43

TABLE 3

Subject	Condition	Date	CO_2 tension	O_2 tension	Total O_2	HbO_2	p_{O_2} (at p_{CO_2} = 80 mm)	
			mm	*mm*	*vols per cent*	*per cent*	*mm*	
D W R Male 30	Normal subject	June 23	air	air	21.4	100.0	—	Total CO_2, oxygenated blood (true serum) (at p_{CO_2} = 80 mm.) = 77.3 vols per cent, pH_s = 7.24
			80.1	32.3	9.5	45.0	32.3	Cell volume = 42 per cent
			79.3	51.1	15.7	74.0	51.3	$\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}} = 0.48$
			78.1	17.1	3.3	15.0	17.3	
			79.0	76.4	18.8	89.0	76.7	
		July 8	air	air	20.6	100.0	—	Total CO_2, oxygenated blood (at p_{CO_2} = 80 mm.) = 63.5 vols per cent, pH_s = 7.24
			116.9	21.6	3.8	18.7	18.9	
			79.9	41.9	12.6	62.1	41.9	
			81.1	61.4	16.8	83.0	61.1	
			80.2	85.3	18.8	92.5	85.3	
A O Female 39	Pernicious anemia	June 19	air	air	13.2	100.0	—	Total CO_2, oxygenated blood (at p_{CO_2} = 80 mm) = 63.6 vols per cent, pH_s = 7.21
			74.8	17.4	2.2	17.3	18.0	Cell volume = 27 per cent
			80.5	51.7	9.5	73.2	51.6	$\frac{\text{Oxygen capacity}}{\text{Cell vol per cent}} = 0.46$
			78.2	33.0	5.5	42.5	33.6	
			76.3	86.9	12.4	95.9	88.4	
W B Male 38	Myelogenous leukemia, secondary anemia	May 5	air	air	10.2	100.0	—	Total CO_2, oxygenated blood (at p_{CO_2} = 40 mm) = 36.0 vols per cent pH_s = 7.21
			47.2	63.5	8.0	80.4	61.7	Cell volume = 55 per cent (large fraction was white blood cells)
			41.7	7.5	0.4	4.1	7.5	
			42.9	40.1	5.4	54.6	39.5	
			43.5	22.6	2.3	22.7	22.3	

are all at a definitely lower level As far as these data are concerned, therefore, the probability is high that the condition of anemia is associated in some way with a lowering of the oxygen dissociation curve, when the pH_s is in the region of 7 64

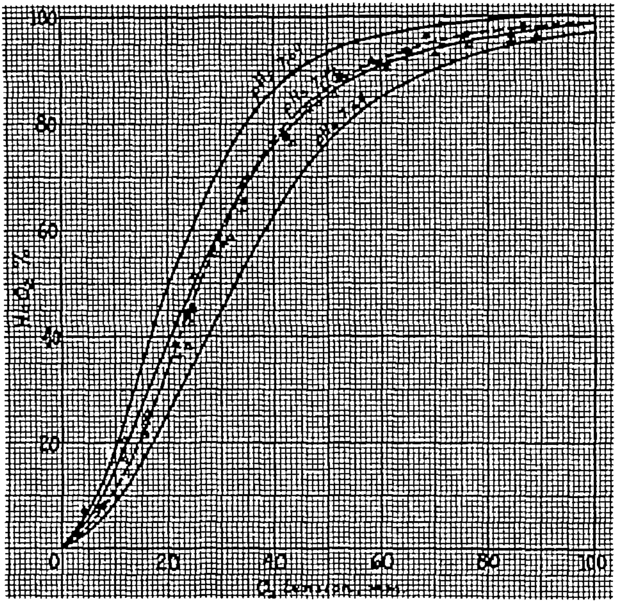

FIG 1 OXY HEMOGLOBIN DISSOCIATION CURVES AT pH_s 7 44 (CO_2 TENSION APPROXIMATELY 40 MM)

Drawn curves from data of Bock, Field, and Adair Heavy dots, normal control Triangles (△) pernicious anemias Plus marks (+), secondary anemias

This can be more clearly shown if the points are plotted logarithmically (on the principle of Hill's equation), with coördinates log $\frac{Hb}{HbO_2}$ and log p_{O_2} This has been done in figure 4, with a curve

TABLE 4

Subject	Sex	Age	Condition	Date	Blood counts		Transfusions	
					Red blood cells	Hemoglobin	Date	Amount
M C	M	62	Pernicious anemia	February 12	600,000	18	February 12	800
				15	900,000	26		
				27	1,300,000	35		
A O	F	38	Pernicious anemia	April 16	700,000	14	April 17	800
				27	1,500,000	20	27	700
				May 21	1,400,000	27	May 27	800
				June 1	2,600,000	30		
				5	3,200,000	42		
C G	F	67	Pernicious anemia	March 25	1,300,000	40	March 27	500
				April 5	1,600,000	60		
H St.	F	49	Pernicious anemia	March 22	1,700,000	30	March 8	800
				May 24	2,900,000	45		
				June 1	3,100,000	42		
H. Sa	M	39	Pernicious anemia	February 13	2,200,000	63		
H. Sm	F	78	Pernicious anemia, chronic cholecystitis	April 28	1,500,000	35	May 6	540
				May 18	2,500,000	50	15	700
V S	F	41	Hematemesis, secondary anemia	April 21	2,300,000	40	April 29	500
				28	2,800,000	35		
P L	M	38	Chronic nephritis, secondary anemia	May 6	3,800,000	70		

W B	M	38	Myelogenous leukemia, secondary anemia	May 7	3 800,000*	60		
M J	F	52	Polycythemia vera	April 17	9,000,000	120		
V G	F	31	Menorrhagia, secondary anemia	June 18	2 500 000	20		
				23	1,800 000	40		
				26	3 000 000	35		
				July 1	3 500,000	45		
M S	M	30	Bacterial endocarditis, secondary anemia	June 6	2 400 000	30		
				22	2 300 000	40		

* W B C. 700 000 myelocytes 51 per cent.

drawn through the points of normal blood, and another through those of the anemic bloods The anemia curve is throughout its course lower than the normal

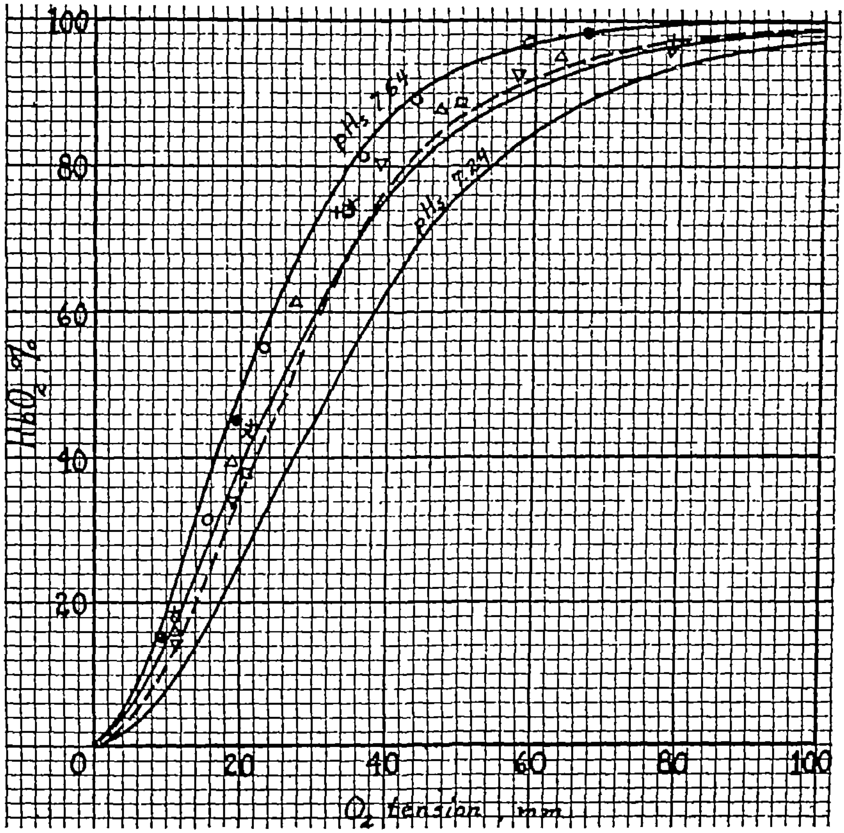

FIG 2 OXY-HEMOGLOBIN DISSOCIATION CURVES AT pH_s 7 64 (CO_2 TENSION APPROXIMATELY 20 MM)

Drawn curves from data of Bock, Field, and Adair Circles, normal control Heavy dots, normal control blood "diluted " Squares and triangles, pernicious anemias Crosses and plus marks, secondary anemias

To summarize, the data which we have obtained indicate that at pH_s of 7 24 and 7 44 there are no large consistent differences between the oxy-hemoglobin dissociation curves of normal and of anemic whole bloods, but that at pH_s of 7 64, the anemic curves are at a lower (more "acid") level than those of normal blood

One would not expect simple dilution of the blood with serum to be responsible for a lowering of the curves, and this was easily shown to have practically no such effect A sample of normal

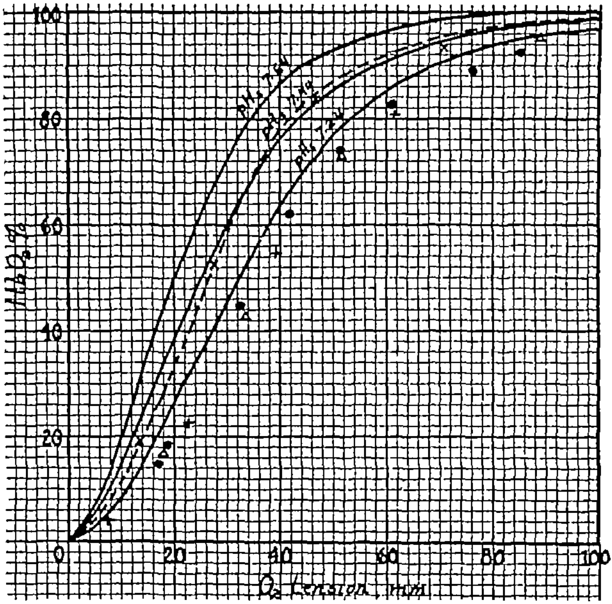

FIG 3 OXY HEMOGLOBIN DISSOCIATION CURVES AT pH_s 7.24 (CO_2 TENSION APPROXIMATELY 80 MM)

Drawn curves from data of Bock, Field, and Adair Heavy dots, normal control. Triangles primary anemia Plus marks secondary anemia Crosses are points on the curve of a patient with polycythemia vera, at CO_2 tension of 40 mm

oxalated blood was centrifuged, a part of the cells mixed with the whole of the serum, and a dissociation curve determined for this diluted blood The points, given in table 2, "diluted blood," and charted in figure 2, fell along the normal whole blood curve

If instead one were to assume a concentration of the hemoglobin within the blood cell, a change, of the type found in our alkaline

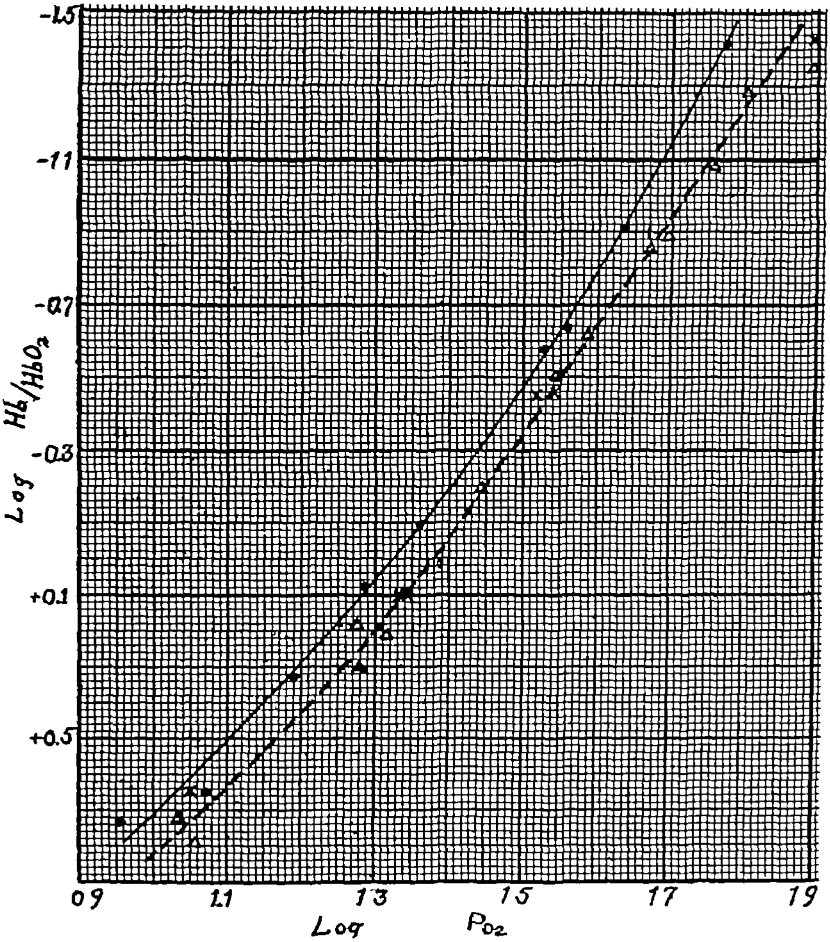

Fig 4 Oxy-hemoglobin Dissociation Curves of Whole Blood at pH_s 7 64, Plotted Logarithmically

Heavy dots and continuous curve, normal control blood Triangles, pernicious anemias Crosses, secondary anemias Dotted line, average curve for anemic blood

anemia curves, would occur, and the displacement would be greater, the more alkaline the pH_s This would be true because an increase in the hemoglobin concentration within the cell would increase the

Donnan effect, that is, the Van Slyke r would diminish and the difference between the cell pH and serum pH ($pH_s - pH_c$, or $-\log r$) would increase Thus at equal pH_s values, the pH_c of the blood with increased cell hemoglobin would be lower than the pH_c of normal blood The oxygen dissociation curve would therefore be at a lower level Furthermore, the relative lowering would be greater the more alkaline the pH_s the $\frac{-\log r}{pH_s}$ ratio having a steeper slope for blood with increased cell hemoglobin than for normal blood This latter follows indirectly from the large increase in the dissociation of the cell protein (i e $[BP]_c$), when the solution becomes more alkaline We have worked out these effects quantitatively using the Van Slyke, Wu, and McLean formula $r = 1 - \frac{[BP]_c + [HB]_c - [BP]_s}{2([B]_s - [BP]_s)}$, and the data from the four experiments of the same paper, assuming, for the blood with increased cell hemoglobin, values of $[BP]_c$ and $[Hb]_c$ 4/3 times the given normal values These computations give consistent results in all the four experiments, an average set of values is the following from experiment 3 (oxygenated blood)

pH_s	$-\log r\ (= pH_s - pH_c)$	
	Blood with increased cell hemoglobin	Normal blood
7 75	0 32	0 24
7 42	0 21	0 16
7 08	0 12	0 10

Thus, whereas at a pH_s of 7 08, the pH_c of the blood with increased cell hemoglobin is only 0 02 more acid than that of normal blood, at a pH_s of 7 75 there is a difference of 0 08 The differences are probably actually larger than those tabulated, because the pH_c figures of normal blood were determined in these experiments by Van Slyke, Wu and McLean from the $\frac{[HCO_3]_c}{[HCO_3]_s}$ ratios, and these ratios were considerably lower in most cases than the r values as determined by the formula for r given above As we have said, we used this formula to determine the pH_c values of the blood with increased cell hemo-

globin That the true $\frac{[H^+]_s}{[H^+]_c}$ ratio (or, more accurately, the ratio of the activity coefficients) is not equal to $\frac{[HCO_3]_c}{[HCO_3]_s}$, but is considerably less, has been shown recently by Van Slyke, Hastings, Murray, and Sendroy (12)

The above calculations are of course only rough approximations the formula for r is itself only approximate, and the suggested changes in values of $[BP]_c$ and $[Hb]_c$ take no account of corresponding changes in other intracellular electrolyte concentrations, which would modify to some extent the percentage oxygen saturation of the hemoglobin The figures given, however, do indicate the direction of the change that might be expected to occur, if concentration of hemoglobin within the cell were one of the conditions prevailing in a given blood The figures also show the considerable increase in this effect when the blood becomes more alkaline

If the concentration of hemoglobin within the cell did occur in anemia, one would expect it particularly in the primary types, with high $\frac{\text{oxygen capacity}}{\text{hematocrit}}$ ratios Our data on this point are not very satisfactory Hematocrit readings were obtained with the blood of two of the primary anemias at pH_s 7 64, giving $\frac{\text{oxygen capacity}}{\text{hematocrit}}$ ratios of 0 52 and 0 50, as compared with 0 47 for our normal control This difference is in the expected direction, but not large enough to account for all the lowering of these two oxygen dissociation curves We obtained a hematocrit reading from one of the secondary anemias at pH_s 7 64, giving an $\frac{\text{oxygen capacity}}{\text{hematocrit}}$ value of 0 43 This does not agree with the concentration hypothesis the dissociation curve of this subject was lower than the normal, and yet the concentration of hemoglobin in the cell, according to the hematocrit, is less than normal All our hematocrit values, however, are at best only approximate, as in our hands this instrument was not reliable For this reason, it is hardly justifiable to use these values for purposes of calculation

Determination of the electrolyte distribution in the blood of the

subjects studied was outside the scope of this investigation reference to the data of Peters, Bulger, Eisenman and Lee (14), showed no indication of any large, consistent variation in the electrolytes of the blood of primary or secondary anemia that might account for low oxygen dissociation curves Gram (15) has shown that the cell chloride concentration in anemia does not vary in any regular manner with the extent of the anemia

We wish especially to express our gratitude to Professor L J Henderson and Dr C D Murray, in collaboration with whom this work was planned, and with whom we had the privilege of discussing our results, and to Dr A B Hastings, for guidance through many technical difficulties

SUMMARY

The oxy hemoglobin dissociation curves of the whole blood of several subjects with anemia, primary and secondary, were investigated at serum pH's of 7 24, 7 44 and 7 64 At the lower pH, values, all curves studied were close to curves of normal blood At serum pH 7 64 the anemia curves were definitely lower than the normal One possible explanation of this fact is discussed

Points on the curve of a patient with polycythemia vera showed no evidence of abnormality

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THE RELATION BETWEEN THE BLOOD UREA CONCENTRATION AND THE AMOUNT OF FUNCTIONING RENAL TISSUE[1]

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The concentration of urea in the blood is dependent upon the rate of urea formation and the rate of urea excretion Urea formation varies with the protein content of the diet and with the rate of protein metabolism while the rate of urea excretion is influenced by many factors (1) As a result the blood urea concentration normally fluctuates through a considerable range of variation However, unless under exceptional circumstances, the upper limit attained is comparatively low so long as there is no reduction in the amount of functioning renal tissue The marked increases in the concentration of urea in the blood which are seen in the terminal stages of Bright's disease when the amount of functioning renal tissue is presumably greatly reduced occur too often to require comment but concerning the degree to which the amount of renal tissue must be reduced before an increase in the blood urea concentration over the normal limits ensues nothing definite is known It is even questionable whether the transient increase in the blood urea concentration which follows the removal by operation of half of the renal tissue of the body (2) can be ascribed to the reduction in kidney substance Such an increase might well be a result of an acceleration of protein catabolism and might occur after any sufficiently severe operative procedure In an attempt to throw some light on these questions a study has been made in a group of patients of the relation between the degree of reduction in the amount of functioning renal tissue and the degree of increase in blood urea concentration

[1] This work was aided by the Wellington Gregg Fund for the Investigation of Bright's Disease

METHODS

The blood urea concentration was determined in each case on a freshly drawn specimen of venous blood obtained not more than two days before the procedure to determine the amount of functioning renal tissue It was necessary that only a short time should elapse between the two observations, for in some cases the blood urea concentration was increasing rather rapidly Another necessary precaution was that the urea determination should precede and not follow the estimation of the functioning kidney tissue because in most cases urea was administered in this test and there was always the possibility that the blood urea would be higher than usual for several days The blood urea estimation was carried out according to Addis' method (3)

The amount of functioning renal tissue was determined in each patient according to the procedure described by Addis (4) It is briefly as follows At 6 a m on the morning of the test the patient slowly drinks about 1000 cc of water in which urea is dissolved In those instances where the blood urea concentration is between 15 and 25 mgm per 100 cc of blood 15 to 20 grams of urea are given If the blood concentration is already as high as 70 mgm urea per 100 cc of blood no urea need be taken At intermediate blood urea levels appropriate quantities of urea are administered, so that when the first blood is collected it should have a concentration of between 60 and 90 mgm of urea per 100 cc of blood At 7 a m and every hour thereafter until and including 11 a m the patient drinks two glasses (600 cc) of water No breakfast is given Urine is voided every hour, but at 9 a m the time at which urination is completed is noted to within thirty seconds and at 10 a m , 11 a m and 12 noon urine is passed directly into special bottles and the exact time noted The patient is instructed to make each voiding as complete as possible, and the time is taken at the end, and not at the beginning, of urination For women a special commode is used with a large funnel emptying into a removable bottle A blood specimen is obtained at exactly the middle of each of the three hourly periods over which urine is collected Beginning with the first urine collection at 9 a m the entire procedure is carried out in the laboratory A high degree of

accuracy in the timing of the blood and urine collections is necessary The methods (3) used for determining the urea concentration of the blood and urine have proven themselves to be particularly applicable to a test of this nature

Under the conditions which have been described the rate of urea excretion is usually governed by only two factors, the concentration of urea in the blood (5) and the amount of secreting tissue in the kidney (6) The ratio, $\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc. blood}}$, is then a measure of the amount of secreting tissue in the kidney After correction for the

TABLE 1

Clinical diagnosis	Number of cases	Number of observations
Hemorrhagic Bright's disease		
Initial stage	3	5
Latent stage	10	13
Active stage	22	30
Terminal stage	10	15
Degenerative Bright's disease		
Cryptic	10	18
Bacterial	2	3
Arteriosclerotic Bright's disease	8	8
Miscellaneous		
Polycystic kidneys	2	2
Pyonephrosis	1	1
Orthostatic albuminuria	2	2
Single kidney	1	1

theoretical body surface corresponding to an individual's height and age this ratio is expressed as a percentage of an average ratio determined on a large group of normal individuals and corrected to their body surface The final figure thus obtained expresses that percentage which the functioning tissue that they possess is of the expected normal amount

When the procedure which has been described is properly carried out with the necessary attention to detail the amount of renal tissue found for a normal individual is very close to that which would be expected (7) from the sex, age, and body weight By weighing the kidneys of rabbits after the completion of this test it has been shown

that the actual amount of functioning renal tissue varies in direct proportion to the magnitude of the ratio (8) If on the other hand the procedure detailed above is not strictly adhered to one may easily conclude as Stander, Duncan and Moses (9) have, that this ratio

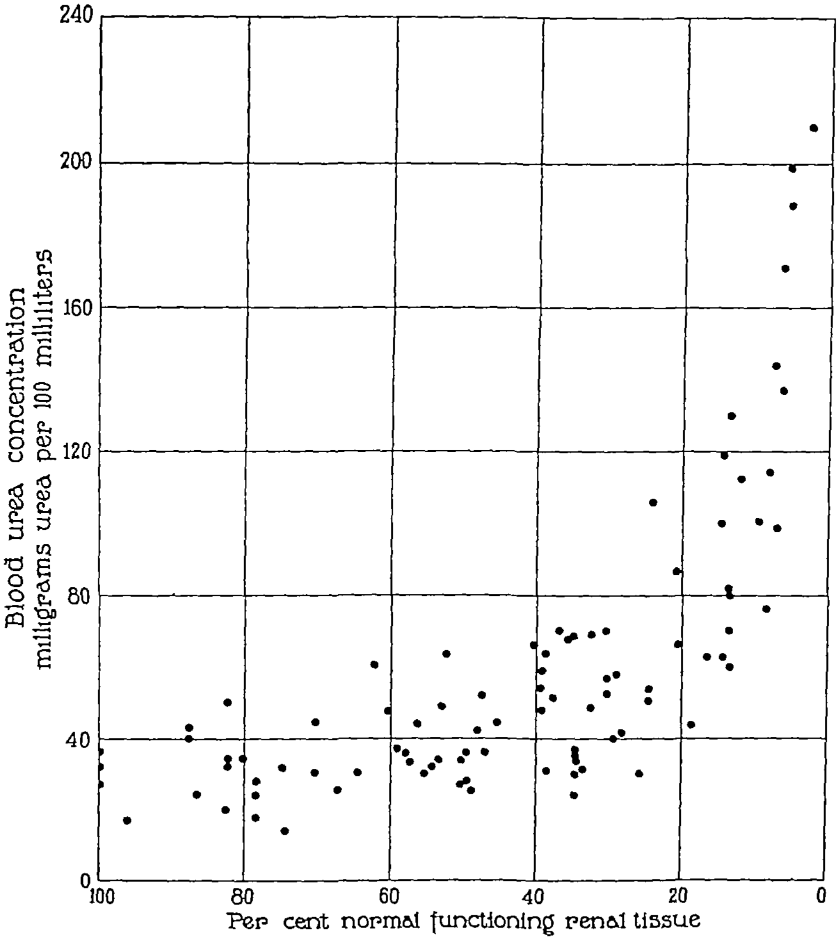

FIG 1

"varies between wide limits" and shows a "lack of uniformity in the values" obtained In this instance since neither water nor urea were administered the authors failed to observe the essential condition of the test, that the kidney should be placed under circumstances which call for great activity in urea excretion They made only a single

observation and even its accuracy is doubtful for the urine collections were left to nurses, a procedure quite out of the question in quantitative work of this nature

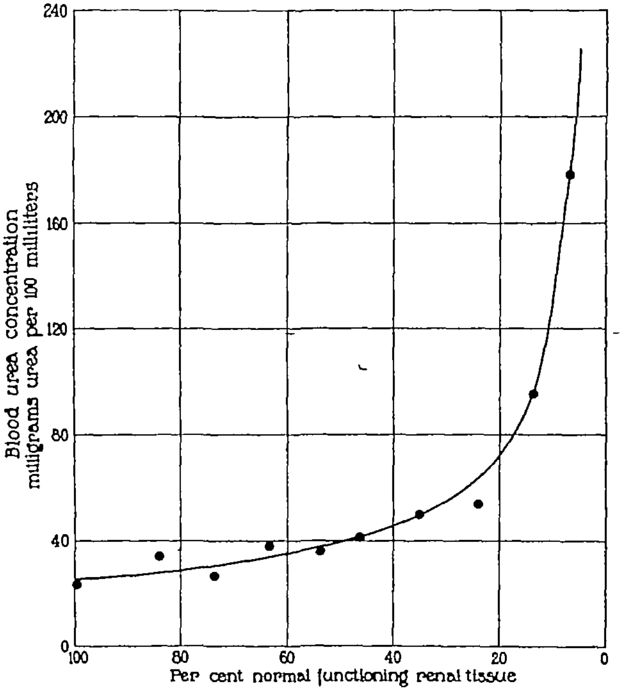

FIG 2

RESULTS

The distribution of the cases from which observations both of the blood urea concentration and of the amount of active kidney tissue were obtained is given in table 1 Practically all of them were indi-

viduals suffering from Bright's disease and of these the majority were in some stage of the hemorrhagic type The higher blood urea observations were all from the two individuals with polycystic kidneys and from the groups with active and terminal hemorrhagic Bright's disease The only observations excluded are those from a few patients in whom the administration of urea and water failed to produce diuresis

In figure 1 the individual blood urea concentrations have been plotted against the percentage of still functioning renal tissue In table 2 these observations have been arranged in a series of classes

TABLE 2

Averages of the per cent of normal functioning renal tissue and of blood urea concentrations Data from all observations

Number of observations	Functioning renal tissue		Blood urea concentration—mean for class
	Limits of class	Mean for class	
	per cent normal	*per cent normal*	*mgm per 100 cc blood*
4	90–100	99	27
9	80–90	83	35
7	70–80	74	29
4	60–70	63	38
14	50–60	54	36
8	40–50	46	51
18	30–40	35	50
13	20–30	24	55
12	10–20	14	95
11	0–10	6	179

according to the amount of functioning tissue and the averages of each class determined In figure 2 the averages have been charted and a curve drawn through them

CONCLUSIONS

It is evident from the above data that the blood urea concentration increases slightly with any reduction from the normal amount of functioning renal tissue but does not begin to rise markedly until the kidneys are reduced to less than half of their original size Beyond this point the blood urea concentration rises with increasing rapidity to higher and higher levels as the amount of renal tissue is still further

decreased The interesting fact is brought out that a patient with Bright's disease may have a blood urea concentration which is within the limits of normal even though only 50 per cent of the normal amount of functioning renal tissue remains

SUMMARY

The relation between the degree of reduction in the amount of functioning renal tissue and the degree of increase in the blood urea concentration was determined in a group of patients who had a reduction in their functioning renal tissue Practically all of them were individuals suffering from Bright's disease

The blood urea concentration does not begin to rise markedly until the active kidney tissue is reduced to about half of its original amount

The blood urea concentration becomes higher and higher with increasing rapidity as the amount of functioning renal tissue is still further decreased

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DISTRIBUTION OF JAUNDICE IN CIRCULATORY FAILURE[1]

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The appearance of biliary pigmentation (jaundice) of the skin and viscera is a relatively common occurrence in severe circulatory failure. It has usually been considered that the distribution of this pigmentation was of a general character A case was reported in 1925 (1) which showed that this was not always true and since then a number of similar cases have come under examination which have demonstrated that a definite localization of the pigmentation may occur under certain conditions of circulatory failure

Case 1 A man with chronic valvular disease of the heart, (aortic stenosis and regurgitation, mitral regurgitation), tricuspid insufficiency, pulsating liver, myocardial failure, dependent anasarca and localized jaundice, death six days after admission[2]

History A white man, aged 37, with a history of recurring attacks of acute rheumatic fever and circulatory insufficiency On December 15, 1924, the dyspnea suddenly became more troublesome and edema of the feet and legs rapidly appeared. On December 20th jaundice of the face, upper part of the body and sclerae appeared

On examination on February 1, 1925, he was found to have the signs of aortic and mitral disease and pronounced evidence of tricuspid insufficiency with positive pulsation of the veins of the neck and pulsation of the liver which were both palpable and visible There was edema of the feet, legs, genitalia, back and abdomen up to the level of the nipples (fig 1) Over this area the skin was white without pigmentation while above this line the jaundice was an intense yellow color Blood pressure was 138 mm. Hg systolic and 48 mm Hg diastolic. There was periodic breathing and there were many fine moist râles at the bases of both

[1] Presented in abstract before the American Society for Clinical Investigation, May 3rd, 1926

[2] This case was reported in the Canadian Medical Association Journal, 1925, xv, 402

lungs There was little sputum not blood-stained The urine contained albumin, bile pigments and many casts The blood showed a moderate nitrogen retention, the Wassermann reaction was negative, the van den Bergh test showed a strong direct and indirect reaction The electrocardiogram revealed a regular sinus rhythm with the auriculo-ventricular conduction time delayed (0 23 second); intraventricular conduction time was also delayed with the "T" wave opposite to the main deflection in each lead, suggestive of a right bundle branch lesion The edema fluid from the leg gave a negative direct and a very faint indirect van den Bergh reaction The patient died six days after admission

Necropsy findings Productive and sclerotic endocarditis of aortic valve with stenosis and insufficiency, productive endocarditis involving the mitral valve and its chordae tendinae, hypertrophy and dilatation of the heart, productive pericarditis, productive pleurisy, red infarct of the lung, and advanced venous stasis of the liver

Case 2 A man with auricular fibrillation, mitral regurgitation and stenosis, hypertrophy of the heart, severe myocardial failure with generalized dependent anasarca and jaundice of the upper part of the body Died

History A white male, aged 33, who had been admitted to the Hospital on two previous occasions and gave a history of recurring attacks of circulatory failure but no history of rheumatic or syphilitic infection Since his discharge from Hospital on December 3, 1924, he had remained in fairly good health until about the middle of May, 1925, when he noticed swelling of the feet, particularly at night This gradually became worse and he suffered from severe dyspnea and palpitation on exertion Then short periods of paroxysmal coughing developed The edema progressed until it extended to the back and abdominal wall

On examination on August 17, 1925, he was found to have signs of mitral stenosis with regurgitation and auricular fibrillation There was pronounced edema in the feet, legs, back and abdominal wall The lungs showed fine crepitations at the end of inspiration at the base of the left lung, the respirations were regular and he suffered from orthopnea The blood Wassermann reaction was negative and there was slight nitrogen retention The liver was palpable but not pulsating and there was no evidence of pulsation in the veins of the neck

The patient's condition continued with slight periods of exacerbation and remission for many weeks

Early in December, 1925, there was a very pronounced increase in his symptoms The heart rate was between 140 and 160 per minute and further digitalis therapy was considered inadvisable on account of evidences of myocardial intoxication as demonstrated by the electrodardiograph On December 5th acute symptoms of tricuspid insufficiency developed, with positive pulsation of the veins of the neck and pulsation of the liver The edema had increased to a pronounced degree On the 7th of December jaundice developed in the upper part of the body above the line of the edema including the face and the sclera There was edema of the

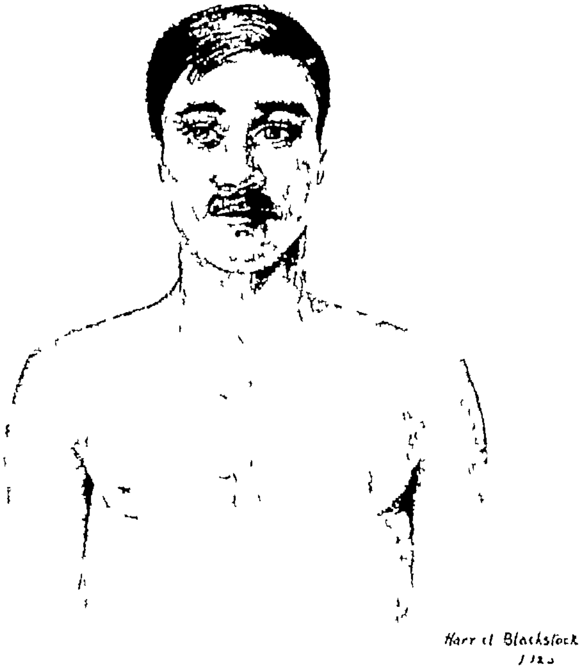

Fig 1 Case 1 Showing Distribution of Jaundice in a Typical Case Here Reported

arms to the insertion of the deltoid muscles Over the edematous area no pigmentation was visible. Examination of the blood showed pronounced direct and indirect van den Bergh reactions and there was bile in the urine On examination the edema fluid drawn from the legs was not pigmented and gave no positive van den Bergh reactions Southey's tubes were inserted in both legs and many liters of fluid were withdrawn by this means But in spite of the icterus becoming more and more intense in the upper parts of the body it did not appear over the edematous areas and it was only when the edema had practically disappeared locally around the site of the insertion of the Southey's tubes that very slight direct and indirect van den Bergh reactions were obtained The patient died on December 12 1925

Necropsy findings The necropsy findings were hypertrophy and dilatation of the heart, infarction of both lungs, hydropericardium ascites and marked venous stasis of the liver

Case 3 A woman with chronic syphilitic myocarditis, chronic mitral valvular insufficiency, auricular fibrillation circulatory failure, general dependent anasarca and jaundice of the upper part of the body Recovered

History A white woman, aged 50, who had been admitted to the Hospital six times since March 1923, the last admission being on April 20 1925 Since her discharge from Hospital on April 29, 1925, she was able to do but little owing to urgent dyspnea on exertion, with a certain amount of edema of the feet and legs in the evening On July 6th she suddenly became conscious of the irregular and rapid cardiac rhythm the dyspnea became more intense and she noticed a pulsating vein on the right side of her neck. The edema of the legs became rapidly worse, extending to the abdomen

On examination on July 15th the patient appeared to be *in extremis* The dyspnea was urgent and there was severe precordial pain The feet, legs, abdominal wall and back were edematous to the nipple line and there was considerable ascites, some cyanosis of the lips and finger tips There was evidence of fluid in both pleural cavities and the heart showed a definite systolic thrill at the apex beat which was 16 cm to the left of the mid-sternal line There was a loud systolic murmur heard both at the apical and tricuspid areas There was positive pulsation of the right jugular vein and there was pronounced pulsation of the liver There was jaundice of the face, sclerae and upper part of the body The electrocardiogram revealed auricular fibrillation On examination of the blood there was a positive Wassermann reaction and the direct and indirect van den Bergh reactions were both positive The urine contained bile pigments but an examination of the ascitic fluid failed to show the presence of bile pigments as determined by the van den Bergh reactions

Under treatment the patient made a rapid recovery The signs of tricuspid insufficiency and jaundice disappeared while the edema subsequently became much less

Case 4 A man with severe myocardial failure, mitral insufficiency, aortic insufficiency (?), dependent edema and jaundice of the upper part of the body Died

History A white man, aged 40, who had been admitted to the Hospital on two previous occasions suffering from circulatory failure After discharge from Hospital on October 15, 1925, he continued in fairly good health Three days before admission (December 13, 1925) he developed edema of the legs, the shortness of breath became exaggerated, he developed orthopnea and was confined to bed

On examination the patient was found to have signs of circulatory failure with mitral insufficiency The diagnosis of aortic insufficiency was in some doubt Electrocardiogram showed a regular rhythm, 90 per minute, auriculo-ventricular conduction time 0 245 second Examination of the blood showed a slight nitrogen retention, and the Wassermann reaction was negative There was pronounced dependent anasarca extending to the nipple line, no edema of the arms The liver was palpable but not pulsating

His condition remained unchanged until January 17, 1926, when he suddenly developed pronounced dyspnea with precordial distress He was found then to be suffering from acute tricuspid insufficiency as shown by pulsation of the veins of the neck and pulsation of the liver Two days later there was jaundice of the upper part of the body above the line of edema, the face and the sclerae, while the edema of the dependent parts had much increased Bile appeared in the urine and both the direct and indirect van den Bergh reactions in the blood were positive The edema fluid showed no direct or indirect van den Bergh reaction The patient died on January 23, 1926

Necropsy was not obtained

Case 5 A man with mitral stenosis and insufficiency, tricuspid insufficiency, severe myocardial failure, jaundice of the upper part of the body and general dependent anasarca Died

History A white man, aged 27, who was admitted to Hospital on December 31, 1925, giving a history of shortness of breath beginning three years previously During these three years he had had repeated periods of failing circulation which would improve on rest in bed In October, 1925, the present exacerbation began with severe dyspnea and palpitation on the slightest exertion and with edema of the feet and legs In November, 1925, the abdomen became enlarged and two weeks before admission he noticed swelling of the wrists and fore-arms There was a history of rheumatic fever in 1914

On examination the patient was found to have signs of circulatory failure with mitral stenosis and insufficiency and auricular fibrillation The liver was 6 cm below the costal margin and the spleen was just palpable There was marked cyanosis of the nose, lips and cheeks, no pulsation of the veins in the neck or of the liver Examination of the blood showed a Wassermann reaction to be negative and there was no nitrogen retention The van den Bergh reactions were both negative There was no anemia The electrocardiogram showed auricular fibril-

lation with numerous ventricular extrasystoles sometimes appearing as pulsus bigemini, while at other times the extrasystoles occurred in groups of three or four in succession With rest in bed and suitable treatment he improved somewhat, but on January 16th there was a sudden onset of increased dyspnea and cyanosis, with the appearance of a positive pulse in the veins of the neck and pulsation of the liver, and a loud to-and fro murmur was to be heard at the lower end of the sternum On January 20th there was an obvious icteroid tinge to the face, sclerae and upper part of the body above the nipples The edema which had been constantly present since admission extended to the line of pigmentation The ascites increased rapidly and on repeated occasions aspiration was required Examination of the blood revealed a positive direct and indirect van den Bergh reaction and there were bile pigments in the urine These were confirmed on repeated occasions but at no time was there a positive reaction in the ascitic fluid although a very faint indirect reaction was sometimes found His condition continued practically unchanged except that the jaundice gradually became more and more pronounced, although occasionally there appeared to be remissions when the signs of tricuspid insufficiency were not so conspicuous On March 12th petechial hemorrhages became evident on the upper surface of the fore arms and chest and the patient died on March 28th.

Necropsy was not obtained.

Case 6 A man with severe myocardial failure, mitral insufficiency, auricular fibrillation, dependent anasarca and jaundice of the upper part of the body Died

History A white man, aged 32, who had been admitted to Hospital on one previous occasion, May 10, 1923, with similar complaints He had had two attacks of acute rheumatic fever previously After his discharge from Hospital he was unable to work but continued in fairly good health until two weeks before admission when the symptoms of circulatory failure suddenly became acute There was pronounced edema of the feet and legs which extended to the back, with swelling of the abdomen, which swelling was most pronounced on the right side where there was acute abdominal pain and tenderness A week later it was noticed that he had jaundice of the face, sclerae and upper part of the body This was still present when he was admitted to the Hospital on January 6, 1926

On examination the patient was found to have signs of severe circulatory failure with mitral insufficiency and auricular fibrillation There was edema of the legs back and abdomen, with pronounced ascites The liver was enlarged and pulsating while the veins of the neck showed a positive pulse There was jaundice of the upper part of the body face and sclerae, and bile pigments were present in the urine The blood showed a negative Wassermann reaction and considerable nitrogen retention There was both a direct and indirect van den Bergh reaction, while in the ascitic fluid both reactions were negative There was some anemia (3 830 000 red cells 75 per cent hemoglobin, and 14 000 leucocytes) The patient s condition became progressively worse and he died on January 17, 1926

Necropsy findings Necropsy revealed chronic productive (sclerotic) endocarditis of the mitral valve causing mitral stenosis, hypertrophy and dilatation of the heart, productive pericarditis, ascites, hydrothorax, general anasarca and marked venous stasis of the liver, spleen and kidneys

CAUSATION OF THE PIGMENTATION

The cause of jaundice in circulatory failure has been from time to time the source of some discussion This discussion has arisen from the difference of opinion as to whether the hepatic lesion was due to a circulatory disturbance or whether a toxic factor—bacterial or non-bacterial—was responsible Attention was first directed to the hepatic condition in these cases by Oertel (2) in 1904, when he described a lesion which he called multiple non-inflammatory necrosis of the liver with jaundice in chronic cyanosis In brief he found that the process consisted of a multiple, irregular, circumscribed solution of the liver cells, without parenchymatous degeneration or coagulation necrosis, and associated with a corresponding blood and bile stasis in the affected areas In 1906 he described (3) the pathological anatomy of three more cases and in 1910, a fifth case (4) Oertel came to the conclusion that it was not a hepatitis but was most probably due to a mechanical cause in the form of chronic stasis Mallory (5) on the other hand held that the disappearances of the liver cells in passive congestion of the liver was the result of bacterial necrosis Bolton (6), in experimental passive venous congestion of the liver, came to the conclusion that the mechanical factor of stasis was the only cause in these cases

More recently Keefer and Resnik (1925) (7) have again drawn attention to the appearance of jaundice in severe circulatory failure They have drawn attention to the close association of pulmonary infarction with the subsequent appearance of icterus They found in the ten cases which they have reported an apparently close relation between the appearance or the increase of icterus a few days after the occurrence of a pulmonary infarct It appeared to them that this association might be caused by the increase of the anoxemia due to the well-known respiratory disturbances accompanied by anoxic anoxemia which follows pulmonary emboli

In the nine cases which came to necropsy these workers found,

apparently, a condition of the liver almost identical to that originally described in 1904 by Oertel (2) Given chronic passive congestion of the liver due to myocardial insufficiency, they adopted the following hypothesis "It is possible that anoxemia, which is caused by pulmonary and circulatory impairment, resulting from pulmonary infarction, may depress the excretory function of already damaged liver cells to such an extent that jaundice appears" In order to test this hypothesis they carried out a series of experiments on dogs with suitable controls (8) The technique of the experiments in brief was as follows to introduce into the stomach of the dog 4 cc of carbon tetrachloride per kilo of body weight, and after a period of twenty-four hours to produce acute anoxic anoxemia by having the animal breathe nitrogen or a low oxygen mixture Their result led them to conclude "that anoxemia may not only impair the function of the already damaged liver, but it may actually be responsible, at least in part, for the damage" Such a conclusion would seem quite justifiable from their experiments, but, these experiments are not a reduplication of the conditions found in the liver in cases of severe circulatory failure, particularly in those instances where tricuspid insufficiency is present

It is a common observation that enlargement of the liver is one of the earliest signs of circulatory failure In fact it may be present before edema of the more dependent parts is detectable The reason for this is probably to be found in the fact that the liver is the only organ in which the greater part of the blood going to it has already passed through a capillary bed, namely that in the bowel It might be supposed, therefore, that stasis due to a slowing of the circulation would be more easily produced in the liver than elsewhere If this were carried to an extreme degree, interference with the bile secretion might be produced which would be probably further aggravated by anoxic anoxemia Under such conditions it would not be expected that evidence of an obstructive jaundice would be found, but more likely that the blood pigments would be of the type found in hemolytic jaundice where an indirect van den Bergh reaction only is obtained In fact this is the mild type of jaundice found so frequently in circulatory failure without pronounced tricuspid insufficiency

The histological picture in the cases here reported was not that of simple passive congestion or nutmeg liver The engorgement was

more extreme and the destruction of the liver cells more complete The engorgement of the smaller bile ducts was also a conspicuous feature while the engorgement of the hepatic vessels about the periphery of the lobules was greater than could be accounted for by simple venous stasis In four of Oertel's cases and in all of those here reported, tricuspid insufficiency with positive pulsation in the veins of the neck and pulsation of the liver was present It was strongly suggested that this factor of active increase of venous pressure in these veins and in the liver by transmission from the right ventricle is a most important factor in the production of this hepatic condition

The manner in which the jaundice occurs would seem quite obvious from the histological appearance of the lesion In the cases here reported there was direct evidence that the jaundice was due to an obstructive cause in that a positive van den Bergh reaction was always found On the contrary in no case without tricuspid insufficiency was a positive direct van den Bergh reaction found, although in six cases with circulatory failure uncomplicated by dilatation of the right ventricle an indirect van den Bergh reaction was present A further study of cases of circulatory failure has confirmed this original finding

DISTRIBUTION OF THE PIGMENTATION

The distribution of the biliary pigmentation was confined to the head and upper parts of the body In all of the cases there was pronounced anasarca extending up to approximately the level of the nipples The hands and lower fore-arms were usually without pigmentation, although it was often present to some extent above the elbows The pigmentation did not appear in the skin over areas where the edema was present Indeed this was the most striking feature in the appearance of these cases The skin over the edematous areas was, if anything, paler than usual while in the non-edematous areas a deep yellow to greenish-yellow pigmentation was present The line of demarcation was quite clear cut The transition zone from the pigmented to non-pigmented areas was only 2 to 3 cm broad

In those cases where an autopsy was procured the endothelium of all the arteries and veins was deeply stained with bile pigments This was followed into the smallest vessels possible This indicated that the plasma of the blood passing through the vessels contained bile

pigments although the skin was apparently not affected In order to further determine this point blood was drawn from a vein in the leg by venesection in a case with pronounced edema of the lower extremities, and this plasma was also found to be deeply bile stained, although the edema fluid from the surrounding tissues was quite clear

EXAMINATION OF EDEMA FLUID

a Bile pigments The dissociation of the edema and biliary pigmentation made an examination of the edema fluid imperative The edema fluid was withdrawn either by means of cutaneous puncture with a three-cornered needle or through Southey's tubes Every precaution was taken to prevent contamination with blood In those cases where the surface tension was estimated precautions were taken to prevent the fluid from being mixed with cutaneous secretions

In table 1 will be seen the comparative findings of biliary pigment, as estimated by the van den Bergh reaction, in both the serum and edema fluid The cases 1 to 6 are those outlined in the protocols In all there was both a direct and an indirect van den Bergh reaction in the serum while in only three of them was there an indication of any biliary pigments in the edema fluid In two of these (cases 1 and 5) the indirect reaction was faintly positive In Case 2 a faint direct reaction developed as well At this time the greater part of the edema had been drained from the legs by means of Southey's tubes and edema fluid could only be obtained by massaging the legs over large areas surrounding the points of insertion of the tubes

The almost constant absence of biliary pigments in the fluids of edema and ascites would point strongly to the conclusion that for some reason the capillary walls were impermeable to them If this had not been the case it was to have been expected that the relative amounts of pigment would have been approximately the same in both fluids In order to determine whether this was an isolated difference more extensive examinations of the serum and edema fluids were undertaken

b Serum proteins These were not fractionated but the total quantity was estimated This was done by means of a Zeiss dipping refractometer In the serum the total proteins averaged 7 43 per cent while in the transudates they averaged 1 147 per cent It was found, however, that the concentration was not equal in samples taken from

TABLE 1

Comparison of blood serum and edema fluid in regard to van den Bergh reaction and surface tension

	Diagnosis	Van den Bergh*					Surface tension	
		Serum		Fluid			Serum	Fluid
		Direct	Indirect	Direct	Indirect	Source		
							dynes	*dynes*
1†	Aortic and mitral disease	++	+++	0	V F ‡	Leg		
2†	Mitral disease, etc and auricular fibrillation							
	July 12, 1925	+++	+++	0	0	Leg	51 9	54 1
	August 12, 1925	+++	+++	0	0	Leg	52 1	54 2
	September 12, 1925	++	++	V F	V F	Leg		58 2
	October 12, 1925	++	++	V F	V F	Leg	52 4	55 7
	November 12, 1925	++	++	V F	V F	Leg		57 1
3	Mitral disease, syphilis and auricular fibrillation	++	++	0	0	Ascites	51 0	54 5
4†	Aortic and mitral disease	++	++	0	0	Leg		
5†	Mitral disease, myocarditis and auricular fibrillation	++	++	0	V F	Ascites	56 4	55 25
6†	Mitral disease and auricular fibrillation	++	++	0	0	Leg		
7	Diabetes mellitus and circulatory failure	0	+	0	0	Scrotum	52 13	45 7
				0	0	Leg	52 13	53 4
				0	0	Pleura	52 13	52 0
8	Nephritis, chronic	0	0	0	0	Leg		56 4
9	Liver and sub-phrenic abscess with pressure	0	0	0	0	Leg	56 0	52 6
10	Myocarditis, chronic and auricular fibrillation	0	0	0	0	Leg	55 3	56 5
				0	0	Peritoneum	55 3	52 3
11†	Mitral and aortic disease and syphilis	—	—	—	—	Leg	54 35	53 35
12	Cirrhosis of liver	+	+	0	0	Ascites		
13	Aortic and mitral disease and auricular fibrillation	0	+	0	V F	Ascites		
14	Chronic myocarditis and auricular fibrillation	0	+	0	0	Leg		

15	Cardio-renal disease	0	0	0	0	Leg		
16†	Chronic nephritis	0	0	0	0	Ascites		
17	Arterio-sclerosis and syphilis	0	+	0	0	Scrotum		
18†	Cardio-renal disease	0	0	0	0	Leg		
19	Auricular fibrillation	0	6 66	0	0	Leg	53 3	57
20	Cirrhosis of liver	0	4 5	0	V.F	Ascites	51 9	51 8
21	Auricular fibrillation	0	0	—	—			

* The van den Bergh reaction was performed according to the method of McNee and Keefer (9)

† Died.

‡ V F Indicates very faint reaction, not sufficient to estimate quantitatively

different regions In six cases where the fluid was obtained from a serous cavity (peritoneum or pleura) the concentration on the average amounted to 2 057 per cent (varying from 0 97 to 3 64 per cent) In only two of these was the concentration of proteins in the serous fluid greater than 1 5 per cent and in both of these (Cases 5 and 13) there was a very faint van den Bergh reaction found in the fluid The fluid obtained from the subcutaneous tissues had a comparatively low protein content, the average being 0 465 per cent

c *Crystalloids* A further study was made to compare the amounts of sodium, potassium, magnesium, calcium, non-protein nitrogen, urea, creatinin and uric acid in the blood serum and edema fluid In so far as these substances were concerned it was found that there was practically a normal balance between the two fluids in all cases It was considered, therefore, that there was no interference with the diffusion of these substances through the permeable membranes separating the blood stream from the tissue spaces and cavities This confirms the findings of previous workers

d *Bile salts* In view of the dissociation of biliary pigmentation and edema it was deemed advisable if possible to determine the presence or absence of bile salts in these fluids We had no reliable chemical method for estimating these salts In spite of the finding of du Nouy that it required relatively large quantities of sodium glycocholate or taurocholate to effect the surface tension of serum it was decided to make comparative observations of the surface tension of the blood serum and edema fluid of cases with anasarca and jaundice, and also of those without jaundice

The surface tension of the serum and edema fluid in ten cases will be found in the table It was found that the differences were so slight as to be possible of explanation by other factors than a variation in the concentration of bile salts We have no evidence at present, therefore, to lead us to a conclusion as to whether such salts pass into the edema fluid or not

SUMMARY

It would seem probable that in circulatory failure there are two types of jaundice, one analogous to the so-called hemolytic variety where there is either an excess of the precursor of the bile pigments

produced in the spleen or an inability on the part of the liver to transform the precursor into bile pigments Such cases are those giving an indirect van den Bergh reaction in the blood serum It is in this type that any increase in the anoxemic state of the liver would be expected to accentuate the impairment of hepatic function and thus promote an increase of the jaundice On the other hand there is the obstructive type of jaundice where, although the bile pigments are formed from their precursor and secreted into the bile capillaries, they are prevented from passing to the larger ducts The bile pigments (in their completed form which is different from their precursor) are then apparently reabsorbed into the hepatic circulation In such cases it would be expected that the direct as well as the indirect van den Bergh reaction would be positive This is what occurred in the cases reported above

The manner in which jaundice is produced in circulatory failure would seem reasonable of explanation Its peculiar distribution and the absence of the pigments in edema and ascitic fluid is not so clear Two hypotheses present themselves, (1) that the permeable membrane between the capillary blood stream and the tissue spaces is impermeable to bile pigments, and (2) that there is such a gross interference with the blood flow through the tissues in circulatory failure that the contents of the tissue spaces remain uninfluenced by changes in the character of the blood plasma If the second hypothesis were the correct one it would be expected that there would be a lack of equilibrium in other substances This has been found to be the case only in regard to the proteins It is suggested therefore that an important determining factor in establishing this equilibrium is the size of the molecule In other words that the membrane between the blood and the tissue spaces is impermeable to substances with as large a molecular structure as proteins and bile pigments This, however, is not absolutely the case in that edema fluid although poor in proteins, as compared to the blood plasma, still does contain them to a moderate degree and at times in a concentration of 50 per cent of the plasma

The presence of bile pigments varies in different secretions They are found in the urine but not in the spinal fluid,[3] milk or saliva The

[3] In children bile pigments may be found in the spinal fluid and the meninges may be stained but this has never been reported in adults Further bile pigments and bile salts have been found in the contents of abscesses in cases of jaundice

reason for this selective action is not clear On the other hand the pigmentation of the skin in jaundice would appear to be due to the disposition of bile pigments in the cellular elements rather than to a diffusion of the pigments into the inter-cellular spaces Microscopic examination of the skin and other tissues shows the cells themselves to contain deposited bile pigments If the bile pigments were not in solution in the inter-cellular spaces it would explain the isolated finding that jaundice of the skin may occur in edematous areas provided the jaundice antedates the occurrence of the edema In this one instance *the skin was pigmented while the edema fluid was free of bile pigments*

It would appear that with our present knowledge an adequate explanation of the absence of bile pigments in edema and serous fluids is not yet possible

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STUDIES ON THE VELOCITY OF BLOOD FLOW

III THE VELOCITY OF BLOOD FLOW AND ITS RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH RHEUMATIC AND SYPHILITIC HEART DISEASE[1, 2]

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INTRODUCTION AND HISTORICAL

Previous studies of the cardiovascular system have been in the main concerned with isolated aspects of the circulation Since an accurate and trustworthy method for measuring the velocity of blood flow had become available, it seemed desirable to learn what changes in the velocity of blood flow occur in cardiovascular disease, and what the relation of such changes might be to other aspects of the circulation

Preceding communications have described the details of the method employed (1), and the results obtained in studying the velocity of blood flow in a group of normal individuals (2) The velocity of blood flow was estimated by injecting active deposit of radium into the cubital vein of one arm, and recording the onset of the ionization effect when the active deposit of radium reached the arterial vessels about the elbow of the other arm In a group of normal individuals the arm to arm circulation times ranged from fifteen seconds to twenty five seconds In a given normal individual, the circulation time, in successive measurements, was found constant within plus or minus two seconds This paper presents a study of the circulation time in patients with cardiovascular disease, and attempts to establish the re-

[1] This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases

[2] Some of the determinations of later date in this and the subsequent communication were performed by means of a detecting device a description of which will shortly be published

lationship between disturbance in the velocity of blood flow and other fundamental aspects of the circulation, such as the cardiac rate and rhythm, arterial and venous blood pressures, and the vital capacity of the lungs

In the past, studies of certain fundamental features of the pathological physiology of compensated and decompensated heart disease have thrown indirect light on the velocity of blood flow Such studies have included observations on venous pressure, vital capacity of the lungs, and minute volume output of the heart The results of the more significant investigations by various observers in these fields may conveniently be summarized under the following headings

Venous pressure

As has been pointed out in a previous communication (2) the wide variation in venous pressure measurements in normal individuals found by different observers necessitated establishing our own normal standards

The most accurate method is that of Moritz and Tabora (3) According to them, normal venous pressure ranges from 1 to 9 cm of water, but other investigators have obtained greater variations Schott (4) in twelve normal individuals observed a range of 15 to 125 mm of water Bedford and Wright (5) observed a range of from 50 to 201 mm of water In a group of normal individuals, the venous pressure, by the method of Moritz and Tabora, was found by us (2) to range from 15 to 100 mm of water Observers who have studied patients suffering from disease of the circulatory system are in fair agreement that congestive failure is attended by a significant rise in the venous pressure Moritz and Tabora found it as high as 20 to 32 cm of water Similarly, Frey (6) in 1902, Hooker and Eyster (7) in 1908, and Frank and Reh in 1911 (8), and Clark (9) in 1915 found a clear correspondence between the abnormal rise in venous pressure and the degree of cardiac decompensation In compensated heart disease, various observers, Fuchs (10), Kroetz (11), Frank and Reh (8) found that it was within the limits of normal

Vital capacity of the lungs

That the vital capacity of the lungs is diminished in cardiac decompensation, and that the diminution bears a close relationship to the

degree of decompensation was established by Peabody and Wentworth in 1917 (12) They measured the vital capacity of a group of normal individuals and established normal standards on the basis of height, weight and sex In studying the vital capacity of a group of patients with various types of heart disease, they found close parallelism between the tendency to experience dyspnea and reduction in the vital capacity

Reduction in the vital capacity may be due in part to the development of engorgement and increased pressure in the pulmonary circulation It is therefore of interest to learn what the relationship between engorgement of the pulmonary circulation, as expressed in the vital capacity, is to engorgement of the peripheral circulation, as expressed in the venous pressure measurements, and what the relationship of both is to disturbance in the velocity of blood flow

Minute volume output of the heart

With a failing circulation one might expect a decrease in the cardiac minute volume output Plesch (13) found no diminution in six determinations on six patients showing fully compensated valvular disease Lundsgaard (14) measured the minute volume output in ten patients according to the nitrous oxide method of Krogh and Lindhard He found it reduced in patients with valvular lesions showing regular rhythm and congestive failure It was normal in patients with compensated circulation and with regular rhythm

In patients with circulatory failure, Lundsgaard (15) in 1918 and Harrop (16) in 1919 found a close relationship between venous oxygen unsaturation in the blood from the cubital vein and clinical evidence of circulatory failure They inferred that a reduced velocity of blood flow in the arm was responsible for the increased oxygen unsaturation in the venous blood in their patients

G N Stewart, (17), by means of the calorimetric method, also found the blood flow diminished in the hands of patients suffering from cardiac decompensation

Velocity of blood flow

E Koch (18) in 1922, injected fluorescein into the vein of one arm, and by observing the time of its arrival in the corresponding vein of

the other arm, found the circulation time prolonged in patients with edema and other signs of failure The circulation time of patients whose circulation was compensated was slightly prolonged in the majority of determinations, and was within the limits of normal in a smaller group of individuals His results indicate only a general relationship between velocity of blood flow and degree of decompensation The limitations of the fluorescein method, and the difficulty of estimating the exact onset of the appearance of the fluorescein is subject to the considerations discussed in a preceding communication (2)

Since previous studies of the blood flow in man have been in the main concerned with isolated aspects of the circulation, and since we wished to study the relationship of various circulatory phenomena both to each other and to the velocity of blood flow as measured by our method, we undertook the following investigation

METHODS

In a group of patients with pathological signs and symptoms of the circulatory system, careful histories and physical examinations were made The height, weight and vital capacity were ascertained The ventricular rate was counted before and after measurement of the velocity of blood flow Electrocardiographic tracings were frequently taken to elicit further evidence of cardiac abnormality In some patients who exhibited abnormal rhythm, electrocardiographic tracings were taken during the time of the test The venous pressure was measured immediately before the active deposit of radium was injected The blood and urine were examined The velocity of blood flow from the cubital vein of one arm to the cubital arterial vessels of the other arm was measured The procedure used in measuring the velocity of blood flow was that described in a previous communication (1)

The results of these measurements are presented below The findings are tabulated according to the etiology of the disease regardless of the state of compensation A short abstract of the history and physical examination with especial reference to the cardiorespiratory system is appended Positive findings are given, and negative data are omitted We have correlated the velocity of blood flow with the actual degree of compensation as observed clinically

I THE VELOCITY OF BLOOD FLOW AND ITS RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH RHEUMATIC HEART DISEASE

Rheumatic heart disease affords a better opportunity to study certain phases of circulatory pathology than heart disease due to other

causes since the time at which the cardiac involvement commences can often be established by the history of antecedent rheumatic fever The rheumatic infection tends, moreover, to attack the valves, and so produces physical signs which enable one to recognize the valvular damage and the rate of development of subsequent changes But it is common experience that the degree of valvular damage indicated by the physical signs is not necessarily closely related to the symptoms experienced by the pateint In a given individual with regular rhythm, the degree of circulatory disability represents the accumulated effect of both valvular and myocardial damage We have therefore attempted to learn what effect rheumatic fever has on the velocity of blood flow and other related aspects of the circulation independent of any valvular changes by studying a group of patients who had had rheumatic fever, but who showed no physical signs of valvular involvement In contrast to this group of patients we have investigated the effect of rheumatic heart disease after it has involved the valves, and finally we have studied the effect of the rheumatic process after it has, in addition, caused absolute arrhythmia of the heart action

In the analysis of circulatory failure it is of importance to learn whether changes in the arterial and venous pressure, vital capacity of the lungs, and velocity of blood flow which manifest themselves in different types of heart disease always occur in the same sequence or whether they bear a different relation according to the etiology of the circulatory disturbance What these relations are, we have attempted to ascertain

A Patients after acute rheumatic fever but without evidence of valvular damage

We have classified our patients suffering from the sequellae of acute rheumatic fever into three groups (table 1) Group A consists of patients who, at the time of admission to the hospital, suffered from acute rheumatic fever, but who, at the time of measurement of the velocity of blood flow, were free from the signs and symptoms of the acute inflammatory process They presented evidence of valvular lesions The first three patients had recently recovered from acute rheumatic fever The only evidence of myocardial involvement was the irritability of the heart The arm to arm velocity of blood flow was normal or

TABLE 1

The velocity of blood flow and its relation to other aspects of the circulation in patients with rheumatic heart disease

Date	Test number	Name	Diagnosis	Age	Surface area	Temperature	Pulse	Arterial pressure: Systolic	Arterial pressure: Diastolic	*Venous pressure	Injected	Vital capacity	Vital capacity per square meter	Circulation time	Circulation time per square meter
Group A Patients convalescent from acute rheumatic fever but without evidence of valvular damage															
					sq m.	*°F*		*mm Hg*	*mm Hg*	*mm* H_2O	*millicuries*	*cc*	*cc*	*seconds*	*seconds*
June 21, 1926	213	S G	Acute rheumatic fever	20	1 46	n	94	108	54	35	3 0	3,900	2,670	11	8
December 2, 1925	18	R L	Acute rheumatic fever	44	2 03	98 4	66	125	65	50	7 2	2,200	1,000	18	9
November 4, 1926	292	F C	Acute rheumatic fever or infectious arthritis	39	1 52	98 3	88	138	72	−20	4 5	3,300	2,172	14	9
June 22, 1926	218	F G	Rheumatic myocarditis	26	1 67	n	38	124	50	25	5 8	2,950	1,770	28	17
June 23, 1926	221	F G	Rheumatic myocarditis	26	1 67	n	40	112	70	25	6 0	2,850	1,700	29	17
October 19, 1926	267	F G	Rheumatic myocarditis	26	1 67	n	142	120	54	50	5 2	2,000	1,197	31	19
Group B Patients with rheumatic valvular heart disease with regular rhythm															
June 21, 1926	219	T H	Mitral stenosis and insufficiency	53	1 77	n	84	124	60	15	—	2,800	1,580	15	8
October 28, 1926	287	K N	Mitral insufficiency	23	1 74	97 8	88	180	66	—	—	5,000	2,816	15	9
October 28, 1926	283	W O'B	Mitral stenosis and aortic insufficiency	42	1 88	99 2	101	142	42	−10	5 0	3,200	1,702	19	10
June 14, 1926	197	A M	Mitral stenosis and insufficiency	15	1 41	n	74	110	45	−20	3 5	2,450	1,736	19	13
March 16, 1926	167	H B	Aortic and mitral disease	15	1 40	97 8	100	134	30	45	1 6	2,850	1,990	20	14
June 14, 1926	191	J V	Mitral stenosis and insufficiency	29	—	98 4	111	118	72	35	3 5	2,800	—	31	—
August 29, 1925	10	T Th	Myocarditis, mitral stenosis and insufficiency	53	1 70	n	—	148	96		4 3	2,000	1,175	60	36
														65	38
September 1, 1925	11	T Th	Myocarditis, mitral stenosis and insufficiency	—	—	—	—	—	—	—	1 9	—	—	71	41

Group C Patients with rheumatic valvular heart disease with fibrillation of the auricles

September 30 1926	258	D S	Mitral stenosis and insufficiency aortic insufficiency	40	1 60		64	130	85	40	—	2,300	1,430	30	19
October 19 1926	265	S C	Mitral stenosis and insufficiency aortic insufficiency	26	1 5	97 4	75	105	40	42	5 5	2,650	1 766	29	19 3
June 23, 1926	224	S C	Mitral stenosis and insufficiency, aortic insufficiency adhesive pericarditis	26	1 53	n	56	128	64	105	6 9	2,550	1,660	34	22
September 1, 1925	13	F M.	Mitral stenosis and insufficiency	43							10 2			53	
August 28, 1926	12	F M	Mitral stenosis and insufficiency	43			55 65				3 8			55	

* To conform to the level of the right auricle, 50 mm should be added to these figures.

slightly more rapid than that found in normal persons This finding is an objective confirmation of the clinical observation that patients after rheumatic fever just as after other acute infectious diseases often exhibit signs of cardiac hyperactivity with forcible, rapid precordial pulsation, a tendency to low blood pressure, a somewhat increased pulse pressure, flushed face and skin, and an absence of signs of decompensation The subjective complaints of precordial pain and tenderness, and palpitation of the heart may also be interpreted as a result of this overactivity of the heart

Two of the patients, R L and F C (nos 18 and 292), had had previous attacks of rheumatic fever, whereas S G (no 213) was suffering from his first attack We can offer no explanation why in patient R L (no 18) the venous pressure was slightly elevated and the vital capacity was reduced In patients S G and F C (nos 213 and 292), who had both experienced shortness of breath on exertion during the preceding year but in whom the circulation was entirely compensated at the time of test, the vital capacities, the venous pressures and the electrocardiographic tracings were normal In these patients the increase in ventricular rate tended to be associated with a more rapid blood flow, a relationship which is similar to a tendency noted in our previous study of normal individuals (2)

In contrast to these patients, F G (nos 218, 221, and 267) was suffering from chronic myocardial failure without evidence of valvular disease as a result of rheumatic fever experienced several years previously His tests are of particular interest Four months before his first entry, he was troubled by breathlessness and orthopnea He had never noted swelling of the legs He was cyanotic and dyspneic The physical signs of the heart were normal, except that at times a soft systolic murmur was heard over the apex, and there was slight cardiac enlargement The electrocardiographic tracings showed sinus arrhythmia with left ventricular preponderance, T3 inverted, a depressed S-T interval, S3 notched, occasional premature ventricular beats, partial heart block (P-R 0 20 second) The first two measurements were made on successive days when his condition was essentially the same The ventricular rates corresponded closely, inasmuch as they were 38 at the first test and 40 at the second The vital capacities were 2950 cc (1770 cc per square meter) on the first occasion, and

2850 cc (1700 cc. per square meter) on the second His condition improved and he left the hospital Although he refrained from work and felt comfortable at rest, dyspnea on exertion continued A few days before his second entry he suffered a recurrence of orthopnea and was forced to use four pillows On admission there was marked dyspnea and orthopnea The physical signs were unchanged except that the heart rate was rapid and there were squeaking rhonchi over the bases of the lungs The circulation time was thirty-one seconds, or nineteen seconds per square meter of body surface The vital capacity was 2000 cc or 1200 cc. per square meter of body surface Although his ventricular rate was 142, or about three and a half times its previous rate, his circulation time was found to be practically the same as it had been on a previous occasion These observations are an exception to our general findings since his circulation time at the time of the third measurement when the clinical condition was worse was only two seconds longer than that found on two previous occasions The discrepancy may be due to the fact that the ventricular rate at the time of the first two observations was 38 and 40, whereas at the time of the third test it was 142 One week later, the patient developed acute dyspnea, was unable to walk, his heart rate was 120 per minute, venous pulsations in the neck appeared, the liver edge was very tender at the level of the umbilicus It was the general opinion that he had no evidence of valvular involvement and that his condition was one purely of rheumatic myocarditis In this instance, therefore, we had the opportunity to observe in a young patient the uncomplicated effects of damage to the myocardium

B Patients with rheumatic valvular heart disease with regular rhythm

Group B consists of patients suffering from valvular disease of rheumatic origin with regular rhythm The arm to arm circulation times were normal or slightly prolonged with the exception of T Th (nos 10 and 11) whose circulation was severely decompensated at the time of the determination The vital capacities of these patients were reduced, the venous pressures were normal

A comparison of the clinical findings with the results of the circulatory measurements establishes the following relationship Five of these patients, T H (no 219), K N (no 287), W O'B (no 283),

A M (197), H B (no 167), never had suffered congestive failure, their vital capacity was, however, reduced, the arm to arm velocity was within the limits of normal, and the venous pressure was normal W O'B (no 283) typifies our findings in this group He was 42 years of age at the time of the test and had had rheumatic fever at the ages of fourteen and twenty-four He had never been aware of any circulatory disturbance although at the time of a life insurance examination, eighteen years previously, he had been informed that he had aortic and mitral valvular heart disease During the past eighteen years he led an active life as a salesman without restricting his activities He showed the clinical signs of mitral stenosis and regurgitation and aortic stenosis and regurgitation The systolic blood pressure was 142 and the diastolic 42 Although the patient had a definite history of valvular disease for eighteen years, it is noteworthy that his circulatory function was entirely adequate for a fairly vigorous life His normal circulation time is in accord with his functional activity Nevertheless his vital capacity, and similarly the vital capacities of the other patients whose circulation was compensated were definitely reduced

In contrast to the five patients just cited J V (no 191) had been troubled with shortness of breath on exertion in the past, but he showed no evidence of congestive failure The velocity of blood flow was nevertheless reduced Patient T Th (nos 10 and 11) is the only person in this group who shows conspicuous prolongation of the circulation time and marked reduction in vital capacity, it should be observed that, similarly, he is the only one of the group who exhibited signs of congestive failure at the time of the test

The appended abstracts of the histories and physical examinations of these patients show that the site and extent of the valvular involvement varied from patient to patient, and that the degree of valvular involvement did not correspond with the degree of circulatory competence

C *Patients with rheumatic valvular heart disease and fibrillation of the auricles*

The three patients in this group showed, beside unmistakable clinical evidence of valvular damage, fibrillation of the auricles with complete

irregularity of the ventricular rhythm They gave histories of dyspnea on exertion but only one patient, F M (nos 12 and 13), showed physical signs of congestive failure at the time the velocity of blood flow was determined Râles could be heard throughout both sides of his chest, especially at the bases Determinations nos 12 and 13 are repeated tests when his clinical condition was stationary, it should be noted that the conspicuous slowing of the velocity of blood flow is in accord with the clinical findings S C (nos 265 and 224) and D S (no 258) who showed a more rapid velocity of blood flow had regained circulatory compensation at the time of test and their improvement is reflected in the shorter arm to arm circulation times

Discussion

Changes in blood flow may depend then (*1*) on valvular damage, (*2*) on muscular injury, (*3*) on both, and (*4*) on the presence of an abnormal rhythm Our observations demonstrate that it is not the localization or the type of valvular lesion which determines the functional severity of circulatory failure, but rather the capacity of the myocardium to compensate for the increased burden imposed We have not yet studied whether one type of valvular lesion predisposes to earlier myocardial insufficiency than another

In general, the results of the study of patients in group A establishes the fact that rheumatic infections, without valvular pathology, may be associated with normal or increased rapidity of blood flow provided the circulation is compensated If valvular lesions develop, without evidence of circulatory insufficiency, one may find that the velocity of blood flow is normal, the venous pressure is not elevated, while the vital capacity may be diminished

When early symptoms of circulatory insufficiency, such as palpitation and dyspnea on exertion, manifest themselves, the vital capacity is reduced, and the velocity of blood flow is definitely retarded, but the venous pressure may still remain within the limits of normal If, however, signs of congestive failure appear, the venous pressure becomes elevated, and the vital capacity and the velocity of blood flow still further deviate from the normal

This sequence of events in circulatory insufficiency exhibited in the course of rheumatic fever is of both theoretical and practical interest

The facts gathered in the preceding section indicate that the immediate effect of rheumatic infection leads to overactivity of the heart, which with the attendant vasodilatation, results in a tendency to an increased velocity of blood flow It is of particular interest to learn that the velocity of blood flow is within the limits of normal in such patients, and that it may remain so even after the valves have undergone changes sufficient to give unmistakable clinical evidence of their distortion With the development of mitral valvular disease, the vital capacity may be reduced, while the velocity of blood flow from arm to arm is still normal or slightly prolonged The reduced vital capacity in the absence of signs of congestive failure has led to the suggestion that the limitation in the excursion of the lungs may be due to diminished elasticity because of engorgement of the pulmonary vessels under somewhat increased pressure, and is not necessarily referable to the respiratory center This suggestion is in accord with the early appearance of dyspnea in patients with mitral stenosis In some of our patients the diminution in vital capacity occurred while the velocity of blood flow was normal While the arm to arm velocity expresses the speed of blood flow through the arms as well as through the pulmonary circulation, the finding of a normal circulation time in the presence of lowered vital capacity suggests that the blood flow through the upper lung fields may be accomplished with normal speed, whereas engorgement and reduced speed of blood flow occurs in the lower portions of the lung

Since our method enables us to measure only the speed of the fastest particle, we cannot offer evidence to support on this hypothesis all the phenomena which occur But the early reduction in vital capacity, the early appearance of breathlessness, the presence in the early stage of the disease of a normal arm to arm velocity of blood flow, the common clinical experience of finding râles first at the bases of the lungs—all these facts are in accord with the hypothesis that the velocity of blood flow through the upper portions of the lung fields may be normal whereas that through the more dependent portions may be retarded, because of the "sedimentation" (19) of the blood Measurement of the minute volume output of the heart in such patients, and a closer estimation of the pulmonary circulation time, would be of great interest in this connection A later communication will deal more specifically with this question

II. THE VELOCITY OF BLOOD FLOW AND RELATED ASPECTS OF THE CIRCULATION IN PATIENTS WITH SYPHILITIC HEART DISEASE

Whereas rheumatic fever usually attacks the mitral valve, syphilis involves most frequently the aorta and aortic valve In mitral valvular disease, with the engorgement of the pulmonary circulation, dyspnea is an early symptom, whereas in aortic valvular insufficiency dyspnea does not appear until later in the course of the disease when the left ventricle is no longer able to carry on the increased amount of of work Dyspnea is of more serious prognostic significance than the same symptom appearing in patients with involvement of the mitral valve.

Examination of the data in table 2 reveals the fact that the patients exhibit lowered vital capacities, and that the velocity of blood flow was reduced beyond the limits of normal in all patients except in patients J P (no 240), J C (no 293), and T B (no 91) The venous pressure was found slightly elevated or within the limits of normal

It is of considerable interest that in J P (no 240) and T B (no 91), both of whom complained of precordial pain and shortness of breath, the velocity of blood flow was within the limits of normal. Neither patient had had at any time signs of congestive failure The occurrence of these symptoms when the blood flow is normal suggests that in syphilitic aortitis, breathlessness and cardiac pain may be due to a reflex nerve mechanism, and not necessarily to congestion of the pulmonary bed The findings in patients suffering from rheumatic heart disease favor this hypothesis, for it was observed that if dyspnea was present at the time of the test the circulation times were invariably prolonged

Further evidence of the lack of relation of pain and dyspnea on the one hand, and of underlying disturbance in the dynamics of the circulation on the other, in patients suffering from syphilitic heart disease is shown by the results of the tests in J H (no 203) He entered the hospital because of lobar pneumonia He did not show pain, dyspnea, or other signs or symptoms of cardiac decompensation, although the vital capacity was low, and the velocity of blood flow was definitely reduced It is noteworthy that objective measurements of the velocity of blood flow gave evidence of impaired function before

TABLE 2

The velocity of blood flow and its relation to other aspects of the circulation in patients with syphilitic heart disease

Date	Test number	Name	Diagnosis	Age	Surface area	Pulse	Arterial pressure		*Venous pressure	Injected	Vital capacity	Vital capacity per square meter	Circulation time	Circulation time per square meter
							Systolic	Diastolic						
1926					*sq m.*		*mm* Hg	*mm* Hg	*mm* H_2O	*millicuries*	*cc*	*cc*	*seconds*	*seconds*
September 2	240	J P	Aortic aneurysm		1 72	84	140	75	75	10 0	2,500	1,453	17	9 8
November 4	293	J C	Aortic insufficiency	52	1 92	82	162	0	—	4 0	2,750	1,434	20	10 4
January 15	91	T B	Aortic insufficiency	54	1 74	63	150	40	15	4 3			19	11
October 26	276	J C	Aortic insufficiency	52	1 92	70	136	0		5 0	2,700	1,406	22	11 4
June 16	203	J H	Aortic insufficiency	54	1 77	87	124	38	35	3 9	2,950	1,660	26	15
January 27	112	W H	Aortic insufficiency	53	1 69	80	192	0	52	2 6	3,150	1,860	29	17
October 21	271	A S	Aortic aneurysm	57	1 58	89			50	5 0	2,300	1,455	32	20 2
June 14	192	I K	Aortic insufficiency	48	1 67	96	130	48	75	4 5	1,600	958	35	21
September 22	243	W H	Aortic insufficiency	54	1 62	88	110	40	−40	5 4	3,000	1,851	36	22 2
September 2	239	W H	Aortic insufficiency	54	1 66	88							43	25 9
June 28	234	W H	Aortic insufficiency	54	1 66	96	125	50	28	6 9	2,550	1,550	48	29

* To conform to the level of the right auricle, 50 mm should be added to these figures

he himself was aware of symptoms and before any clinical signs appeared, because six months later he entered the hospital, cyanotic, dyspneic, orthopneic and edematous He died five days after admission and autopsy showed the presence of cardiac hypertrophy, aortitis, and aortic insufficiency of syphilitic origin In this instance, therefore, the circulation time was the first sign of heart failure and was therefore of prognostic significance.

The two patients, I K (no 192) and W H (nos 112, 243, 239, and 234) who showed the greatest retardation of blood flow, entered the hospital with pronounced signs of chronic passive congestion I K (no 192), who showed pulmonary congestion and swelling of both legs at entry, improved markedly and when his circulation time was measured he had no edema, no orthopnea and no dyspnea The circulation time was thirty-five seconds, the vital capacity was 1600 cc and the venous pressure was at the extreme upper limit of normal

The other patient, W H (nos 112, 243, 239, and 234), who showed conspicuous retardation of blood flow, is especially interesting for repeated measurements were obtained several times during his stay in the hospital when his clinical condition showed definite changes Previous to his first test he had experienced paroxysmal nocturnal dyspnea for one year On the morning of the test day his circulation was compensated and he was free from breathlessness. The velocity of blood flow was twenty-nine seconds, the vital capacity was 3150 cc On June 28, 1926, the time of the second test, he still experienced pronounced orthopnea and showed edema of the ankles, two features which had not been present at the time of the first test. Clinically, therefore, his condition was worse. His circulation time was found to have become prolonged to forty eight seconds, the vital capacity was reduced to 2550 cc. and the venous pressure was 2 8 cm of water, still within the limits of normal Sixty days later his clinical condition improved, for, though orthopneic, edema of the ankles had disappeared His circulation time was shorter, i.e., forty three seconds Under full doses of digitalis and rest in bed, the shortness of breath disappeared and he was able to walk about the ward and three weeks later, his circulation time was thirty six seconds and his vital capacity, 3000 cc. In short, the circulation time ran parallel to the other signs

Discussion

These observations on syphilitic patients indicate that there is a definite relationship between the degree of circulatory sufficiency and the arm to arm velocity of blood flow, and that the latter measurement is an objective and in general a quantitative index of the state of the circulation Observations before, during and after the disappearance of the signs of chronic passive congestion indicate that the circulation time and the vital capacity may show deviations from the normal before the clinical signs of congestive failure appear In patients whose condition is improving the velocity of blood flow and the vital capacity may increase before the clinical evidences of chronic passive congestion disappear and the patient has regained full circulatory compensation Contrary to our general experience, certain patients with syphilitic aortitis although they exhibit symptoms of breathlessness, precordial pain and lowered vital capacities, nervetheless have normal velocities of blood flow These findings support the opinions of those investigators who believe that pain and dyspnea in patients with syphilitic aortitis may be due to a reflex mechanism rather than to chronic passive congestion

A further discussion of the general aspects of the findings presented in this communication will be given in another paper (Paper V of this series)

SUMMARY

I The velocity of blood flow and its relation to other aspects of the circulation have been studied in patients with rheumatic heart disease We have divided these patients into the following groups

A Without valvular damage 1 Six measurements of the arm to arm circulation time, of the venous pressure, and of the vital capacity were made on four patients and correlated with the clinical findings

2 Three patients showed a normal or slightly increased velocity of blood flow which was associated with clinical evidences of exaggerated cardiac activity following acute rheumatic fever

3 Three measurements of the velocity of blood flow in a young adult who exhibited the symptoms and signs of severe myocardial damage due to rheumatic fever, showed a slightly prolonged velocity of blood flow

B With valvular disease and regular rhythm 1 Eight measurements of the circulation time and related aspects of the circulation were made on seven patients

2 The circulation times were normal, or slightly, or greatly prolonged according to the clinical condition of the patients

3 Patients who had never shown the signs or symptoms of cardiac decompensation had circulation times that were within the limits of normal The vital capacities of these patients tended to be reduced, the venous pressures were normal

4 Our observations indicate that the circulation times in patients with rheumatic heart disease reflect the dysfunction due to myocardial damage.

5 The site and extent of the valvular heart disease varied from patient to patient There is no close relationship between the degree of valvular involvement and the degree of circulatory competence as reflected by the velocity of blood flow

C With valvular disease and fibrillation of the auricles 1 In five measurements of the velocity of blood flow on three patients the circulation times ranged from twenty nine seconds to fifty-five seconds, and bore a definite relationship to the degree of circulatory compensation

II The velocity of blood flow and related aspects of the circulation were studied in patients with syphilitic heart disease.

1 Eleven measurements of the arm to arm circulation time, of the venous pressure, and of the vital capacity were made on seven patients suffering from lesions of the aortic valve.

2 In all patients in this group in whom the circulation time was prolonged beyond the extreme upper limit of normal there was evidence of circulatory failure. The vital capacities were reduced, the venous pressures were normal or slightly elevated The degree of prolongation of the circulation time corresponded to the degree of circulatory failure

3 When cardiac pain and dyspnea, but no signs of congestive failure are present, normal velocity of blood flow may be present This suggests that breathlessness and cardiac pain may, in patients with syphilitic aortitis, be due to a reflex mechanism, and that they are not necessarily due to congestion of the pulmonary bed

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APPENDIX

I. Abstracts of Histories and Physical Examinations of Patients with Rheumatic Heart Disease

213 S G had fever and painful and swollen joints five months previously At time of test, occasional fleeting pains were referable to various joints There was no history of cardiac failure P.E was negative except for a faint systolic murmur over the apex. Heart rate was slightly rapid, 80–95 Diagnosis—acute rheumatic fever

18 R L had had repeated attacks of tonsillitis and swelling of joints during previous twelve years He entered hospital with swollen ankles Later, his knees and right hip became painful and tender P.E —heart sounds were of good quality Both knees and ankles were swollen, hot and tender Hgb 90 per cent W.B C 11,500 Diagnosis—acute rheumatic fever

292 F G For two months there was swelling of the right wrist, spontaneously subsiding He had had a similar attack seven years previously One week previous to entry, red, tender swelling of right wrist and right elbow appeared P.E was entirely negative at time of test. Diagnosis—acute rheumatic fever

218, 221, 267 F G had had numerous attacks of tonsillitis in the past, but there was no history of rheumatic fever Four months previous to tests 218 and 221, he developed gradually increasing dyspnea Orthopnea appeared three weeks before test with occasional pain over the epigastrium. There was no history of congestive failure P.E —apex in the 5th space Left border dullness 12 cm The sounds were regular Systolic murmur heard at apex. Lungs were clear Liver was not palpable There was no edema Electrocardiographic tracing at time of first test showed left ventricular predominance, T3 inverted, S3 notched, depressed S-T interval, occasional ventricular extra systoles These signs may have been due to digitalization After discharge from hospital, patient was unable to work and dyspnea on exertion continued A few days before second entry he became suddenly orthopneic and entered the hospital showing marked arterial pulsations in the neck. The heart action was rapid Otherwise signs were the same as at previous entry There were squeaking râles over chest posteriorly The liver was not palpable and there was no edema of the ankles Diagnosis—rheumatic myocarditis

219 T H had had repeated attacks of swollen and painful joints for thirty-eight years, but no history of shortness of breath or congestive failure P.E—Heart was enlarged Left border dullness 12 cm First sound over apex was loud and booming and the second sound over the pulmonic area was accentuated and loud Short presystolic murmur preceded the first sound Blowing systolic murmur was heard over entire precordium The liver edge was palpated about 4 cm below costal margin at entrance but was not palpated at time of test R B C 4,005,000 Hgb 75 per cent Diagnosis—subacute rheumatic fever with mitral disease

287 K N entered hospital because of pain and swelling of both knees He had had acute rheumatic fever five weeks' duration which responded to treatment by salicylates At time of test there were no joint signs or symptoms P E—heart Left border dullness 11 5 cm from midsternal line in 5th space First sound was accentuated Soft systolic murmur at the apex was transmitted to the axilla There were no diastolic murmurs Diagnosis—mitral insufficiency

283 W O had had rheumatic fever twenty-eight years and eighteen years previously At time of insurance examination eighteen years previously he was told he had aortic valvular disease He never experienced any symptoms referable to the circulatory system and entered the hospital because of acute alcoholic intoxication He was able to lead a vigorous normal life P.E showed a well developed man with conspicuous arterial pulsations in neck vessels Heart was moderately enlarged, with the apex 14 cm to the left of the midsternal line in the 5th space Apex impulse was heaving There were no thrills At apex, first sound was rough and loud, second sound accentuated Short, rough presystolic murmur and soft systolic and diastolic murmurs were heard Loud, long diastolic murmur heard along the left border of sternum and faint diastolic murmur over aortic area Corrigan pulse and Duroziez' sign were present Diagnosis—mitral stenosis and regurgitation, aortic regurgitation

197 A M had no definite past history of acute rheumatic fever No dyspnea or congestive failure P.E showed a presystolic murmur with loud, short first sound, the elbow joint red, tender and swollen Diagnosis—acute rheumatic fever, mitral stenosis and regurgitation

167 H B had had repeated attacks of rheumatic fever for the past ten years There was no history of dyspnea or congestive failure He entered hospital with an acute flare-up of rheumatic fever P.E showed the apex impulse in 6th interspace, left border of cardiac dullness 14 cm from the midsternal line Double murmurs were heard at apex and over aortic area with systolic thrill transmitted to the large vessels of the neck The lungs were normal Liver was not palpated X-ray showed heart enlargement both to the left and to the right R.B C 4,570,000, Hgb 60 per cent Diagnosis—rheumatic endocarditis with mitral stenosis and insufficiency, and with aortic stenosis and insufficiency

10, 11 T Th had had increasing dyspnea and weakness for three years, with several attacks of congestive failure P E showed Cheyne-Stokes breathing, left border dullness 17 5 cm. from the midsternal line in the 6th space Faint systolic blow was heard over the precordium Chest was broad and definitely

emphysematous in type Tender liver edge felt 10 cm. below right costal margin in the nipple line Blood pressure was 148 systolic and 100 diastolic. Numerous râles were heard over both chests Pitting edema of both legs was present. Electrocardiographic tracings showed right bundle branch block. Diagnosis—rheumatic myocarditis, mitral stenosis and insufficiency

258 D S had had shortness of breath, attacks of sharp lancinating pain over the heart for several years, following exertion, which was non radiating and lasted a minute or two There was marked orthopnea One week before entry he coughed up blood streaked sputum P.E showed left border of cardiac dullness 12 cm The apex impulse was felt in the 5th and 6th interspaces The cardiac rhythm was totally irregular Double murmurs were present over the apex and over the aortic area. Râles were heard over the lungs There was edema of both ankles Hgb 75 per cent Diagnosis—mitral stenosis and insufficiency

224 265 S C complained of shortness of breath He had had rheumatic fever in childhood but had been well until nine years previously, when, after pneumonia, he developed moderate shortness of breath for eight months During the six months before entry he experienced slight precordial pain on exertion with shortness of breath and palpitation P E at time of test 224 showed the heart markedly enlarged, and all sounds obscured by murmurs Blowing systolic and diastolic murmurs were heard over the apex, soft systolic and diastolic murmurs over the 2nd interspace A thrill was felt all over the precordium with marked systolic retraction. The heart rate was slow, and the rhythm totally irregular Suggestive Broadbent sign was present. No râles were heard over the chest Liver was not palpable There was no evidence of pitting edema. Hgb 90 per cent The patient left the hospital but was soon troubled by a choking sensation associated with pain in the epigastrium He had frequent palpitation and dyspnea on exertion, and orthopnea for one week before second admission to hospital Three days before this second admission pitting edema was observed over lower legs After admission to the hospital, on rest in bed and digitalis, he showed moderate improvement At time of second test, 265, he was still slightly orthopneic P.E showed heart signs as before noted, and moist râles over left base Diagnosis—rheumatic pericarditis, auricular fibrillation.

12, 13, F M had had dyspnea for three months, orthopnea ten days There was no history of congestive failure P E showed left border of cardiac dullness 14 cm from the midsternal line, systolic and diastolic murmurs and a thrill at apex. There were moist râles over both chests especially at bases Diagnosis—mitral stenosis and regurgitation, auricular fibrillation

II Abstracts of Histories and Physical Examinations of Patients with Syphilitic Heart Disease

240 J P had had occasional slight pain below manubrium with attacks of shortness of breath He felt weak and was unable to do hard labor There was no history of congestive failure P.E was negative except for a systolic murmur

over the base By x-ray, aneurysm of the aortic arch was observed Diagnosis—aneurysm of the aortic arch

276, 293 J C had had shortness of breath, tired feeling, and nocturnal attacks of dyspnea and wheezing There was no history of congestive failure Dyspnea was unusually severe on the slightest exertion P E at time of first test showed marked arterial pulsations visible in the neck, a heaving apex impulse over the 5th space, left border of cardiac dullness 12 5 cm from the midsternal line, systolic and diastolic murmurs over the apex and over the aortic area The systolic murmur was transmitted into the vessels of the neck. Corrigan pulse was present The lungs were clear, the liver was not palpable Wassermann was positive at time of second test, No 293 Patient improved subjectively, and was able to walk about without shortness of breath P.E was as before noted Diagnosis—aortic insufficiency, syphilis

91 T B had had marked dyspnea and cough for nine months but no edema of legs P E (date of test) showed orthopnea, blood-streaked sputum, no signs of edema, pain over aortic region, and cardiac hypertrophy with a diastolic murmur over 2nd left interspace Diagnosis—aortic insufficiency

203 J H entered hospital suffering from lobar pneumonia He gave no history of cardiac decompensation Signs of aortic insufficiency were discovered at routine examination Apex impulse was seen in the 6th interspace The left border of cardiac dullness was 12 cm from the midsternal line Short systolic and long diastolic murmurs were heard over base, especially over left border of the sternum Wassermann test was positive Diagnosis—post-pneumonia and aortic insufficiency

112 W H had had progressive dyspnea with paroxysmal nocturnal attacks for one year, orthopnea and epigastric pain for two weeks before admission P E showed the apex in the 6th space, 12 cm from the midsternal line, and systolic and diastolic murmurs over base Brachial and radial arteries were sclerosed Corrigan pulse was present No signs of congestive failure were present Diagnosis—aortic insufficiency, syphilis

271 A S entered hospital because of dyspnea and abdominal pain five weeks in duration, with sharp, precordial non-radiating pain He noted slight swelling of legs and was troubled by cough He was forced to use two or three pillows at night, but rapidly improved under rest and digitalis P E showed the sclerae slightly jaundiced, and the heart in 5th space 13 cm from midsternal line A double murmur was heard over the aortic area and the tender edge of the liver was felt 3 fingers breadth below right costal margin There was no edema of legs The lungs were normal He could walk on the level without stopping Kahn test was positive Fluoroscopy showed aneurysm of the ascending aorta Diagnosis—aneurysm of ascending portion of arch of aorta

192 I K had had shortness of breath and swelling of legs for four weeks, and orthopnea for two weeks A few days before entry, there was marked swelling of both legs P.E showed a heaving diffuse apex beat with maximum intensity in the 6th space where left border dullness was 12 cm from the midsternal line

Supracardiac dullness over the left 2nd space was 4 cm. To the right of the sternum there was a palpable impulse The sounds were regular and of good quality Over the right of the sternum in 2nd space there were soft systolic and diastolic murmurs Marked edema of lower extremities at time of entrance was noted At time of test there was no dyspnea or edema X ray examination showed shadow of an aortic aneurysm. Hgb 110 per cent R.B C 4,300,000 Diagnosis—aortic aneurysm with probable aortic insufficiency

234, 239 243 W H had had for one year progressively increasing dyspnea, marked at night, and increasing weakness and cough for one month and orthopnea for two weeks P E showed at time of admission respiratory distress with orthopnea the apex impulse in the 6th space, left border of cardiac dullness 13 cm. from midsternal line Double murmurs were heard over the aortic area Tender liver edge was felt 3 fingers below costal margin. Slight edema of both ankles was present At time of 1st test 234 there was marked dyspnea orthopnea, slight pitting edema over ankles At time of 2nd test, 239, there was orthopnea, no congestive failure and he was able to walk slowly At time of 3rd test, 243, his circulation compensated fairly well at rest and he was able to walk He felt stronger Diagnosis—aortic insufficiency, syphilis

TABLE 1

The velocity of blood flow and its relation to other aspects of the circulation in patients with arteriosclerosis and with evidences of myocardial degeneration with regular rhythm

Date	Test number	Name	Diagnosis	Age	Surface area	Temperature	Respiration	Pulse	Blood pressure Systolic	Blood pressure Diastolic	Venous pressure	Injected	Vital capacity	Vital capacity per square meter	Circulation time	Circulation time per square meter
					sq m	°F			mm Hg	mm Hg	mm H_2O	millicurie	cc	cc	seconds	seconds
June 21	215	D C	Myocardial degeneration, emphysema	77	2 04	n	22	54	108	55	• 35	3 0	3,200	1,640	22	11
January 14	71	T H	Arteriocleroses, myocardial degeneration	53	1 82	98 2	24	95	150	80	0 5	4 2	2,100	1,150	25	14
January 9	48	D M	Arteriosclerosis	38	1 76	97 6	20	75	92	58	20	4 8	5,200	2,950	25	14
November 20	17	E L	Moderate arteriosclerosis, myocardial degeneration	51	1 92	98 0	23	75	134	74	58	2 9			29	15
January 13	63	J W	Arteriosclerosis, myocardial degeneration	57	1 60	98 2	26	70	108	72	25	5 1	2,800	1,800	25	15
December 5	21	L C	Moderate arteriosclerosis	44	1 67	98 2	20	60	110	55	45	1 8	3,200	1,900	25	15
															26	16
December 4	20	L C	Moderate arteriosclerosis	44	1 67	98 6	19	62	110	60	50	4 1	3,100	1,850	27	16
December 2, 1925	19	L C	Moderate arteriosclerosis	44	1 67	97 4	18	60	120	80	45	1 7	3,100	1,850	28	17
January 12	57	J W	Arteriosclerosis, diabetes	66	1 58	97 6	18	71	142	86	48	6 8	2,800	1,700	29	18
January 12	58	J W	Arteriosclerosis	64	1 55	97 6	16	71	124	54	−12	6 0	2,200	1,420	29	19
June 14	193	H B	Arteriosclerosis	64	1 60	n	24	68	114	54	−35	5 1	3,100	1,930	30	19
February 12	87	T O	Myocardial senile emphysema, arteriosclerosis	70	1 66	97 2	12	52	124	64	21	2 1	2,700	1,630	32	19

June 16	199	A C	Arteriosclerosis myocardial degeneration	70	1 74	n	26	81	130	76	30	4 0	2 350	1 350	34	19
June 23	223	H. B	Myocardial degeneration arteriosclerosis coronary thrombosis	52	1 66	n	18	60	114	64	65	5 8	2,650	1,500	33	20
December 16 1925	33	J O	Chronic arthritis moderate arteriosclerosis	58	1 71	98 1	22	74	114	65	0 8	3 2	4 400	2 570	34	20
March 16	168	F S	Myocardial degeneration	66	1 94	98 0	19	88	126	58	32	3 5	2,150	1 120	30	21
September 22	242	J B	Myocardial degeneration	57	1 77	96 6	18	64	118	80	−7	4 6	3 750	2 118	39	22
June 14	194	J W	Arteriosclerosis diabetes	66	1 61	n	20	56	125	80	80	5 2	2 800	1 730	37	23
November 4	295	M C	Myocardial degeneration	72	1 46	98 4		62	75		35	4 0	1 550	1 062	39	27
September 22	241	D M	Arteriosclerosis, diabetes	78	1 57	95 2		72	114	50	15	4 8	3 200	2 038	45	28 7
December 29, 1925	36	J G	Myocardial degeneration emphysema L	79	1 63	96 2	18	76	116	65	30	10 6	2 950	1 800	48	29
October 28	284	J S	Arteriosclerosis, cardiac asthma	66	1 57	97 2		100	125	90	35	4 5	2,000	1,273	51	32
October 28	290	L.	Arteriosclerosis, arthritis	60		99		72				5 0	3,000		25	

ages of fifty and sixty years he observed great variation The reduction in some individuals of advanced years is undoubtedly an expression of underlying emphysema, and is not necessarily due to circulatory causes Advanced age in itself does not predispose to reduced velocity of blood flow, for we have found (3) that persons of approximately the same age as the patients here studied may have blood flow velocity within the limits of the normal observed in younger individuals

Inspection of table 1 which includes all patients of the three groups shows that while the circulation times were in general prolonged, this prolongation was not conspicuous Of the eighteen patients studied, only four showed arm to arm velocities of blood flow greater than thirty-five seconds In seven patients, however, the circulation times were between twenty-five and thirty seconds The vital capacities were all definitely reduced except in D M (no 48), in whom it was normal, but whose circulation time was just outside of the normal limits This patient did not give a history of cardiac failure but showed evidence of unusually advanced arteriosclerosis In Group A (table 2) which includes patients without history or signs of congestive failure, there is considerable variation of the circulation time although, in general, its average prolongation runs parallel to the decrease in vital capacity The venous pressures, on the other hand, are, in general, all within the limits of normal, as is to be expected in patients without conspicuous congestive failure The patients of Group B (table 3) who complained of dyspnea on exertion without signs of congestive failure showed greater retardation of the velocity of blood flow and a more marked reduction in the vital capacity than patients of Group A

Five patients (table 4) entered the hospital because of congestive failure On rest in bed, and on administration of digitalis, they improved strikingly so that by the time the velocity of blood flow was measured, edema and dyspnea had disappeared and they showed only moist râles at the bases of the lungs In patients who are regaining cardiac compensation, the increased venous pressure tends to disappear early, followed at first by a return of the velocity of blood flow to normal, and only later by a rise in the vital capacity The time relationship between these three phenomena in patients showing

circulatory improvement is the reverse of that observed in patients with increasing failure The measurement of the velocity of blood flow therefore affords information of prognostic value

While there is a general relationship between the venous pressure, velocity of blood flow, and vital capacity, the results do not permit the formulation of a definite quantitative relationship Whether such a relationship is possible is very questionable The velocity of blood flow from arm to arm reflects the situation existing in the arm, and to a larger extent, in the lungs But the clinical signs of congestive failure may be due to passive congestion of the liver, of the legs, or of other parts of the body That there is a precise quantitative relationship between the velocity of blood flow through the lungs and in each and every other portion of the circulation is improbable Vital capacity measurements, furthermore, do not lend themselves to precise interpretations in persons with generalized arteriosclerosis because of the tendency to pulmonary emphysema

In studying patients with evidences of arteriosclerosis and myocardial degeneration, we have been impressed by the relatively late appearance of dyspnea This may be due in part to the fact that these persons frequently experience weakness as their earliest symptom, whereas patients with rheumatic or syphilitic heart disease whose blood velocity is similarly prolonged do not restrict their activities until compelled to do so by dyspnea. The spontaneous reduction of muscular activity, in patients with arteriosclerosis goes more or less parallel with impairment of heart muscle function so that these patients live within the limits of the functional capacity of their hearts and thus do not show symptoms of cardiac insufficiency The late appearance of dyspnea may also be due in part to the presence of emphysema, for Scott (4) has shown that patients with emphysema are remarkably insensitive to concentrations of carbon dioxide which would be sufficient to cause overstimulation of the respiratory centers of normal persons

B Patients with fibrillation of the auricles

The patients presented here (table 5) showed fibrillation of the auricles without antecedent rheumatic or syphilitic infection, but with signs of advanced arteriosclerosis

The average circulation time of all patients with auricular fibrillation is approximately 100 per cent above the extreme upper limit of normal The conspicuous slowing of the velocity of blood flow is in

TABLE 5

Circulation times and related measurements in patients with fibrillation of auricles and with history of dyspnea but without signs of congestive failure at the time of the determination

Test number	Circulation time	Circulation time per square meter	Vital capacity	Vital capacity per square meter	Venous pressure
	seconds	*seconds*	*cc*	*cc*	*cm* H_2O
30	57	34	3,050	1,800	0 3
31	47	28	3,150	1,870	1 2
69	42	25	2,500	1,500	1 2
74	28	16	2,800	1,560	1 2
76	44	24	3,600	1,960	4 1
226	23	14	3,000	1,820	4 7
247	42	26	1,100	688	−3 0
Average	40 4	23 9	2,743	1,600	1 4

TABLE 6

Circulation times and related measurements in patients with fibrillation of auricles, with history of congestive failure and with signs of congestive failure at the time of the determinations

Test number	Circulation time	Circulation time per square meter	Vital capacity	Vital capacity per square meter	Venous pressure
	seconds	*seconds*	*cc*	*cc*	*cm* H_2O
23	55	29	3,100	1,650	7 0
90	46	38	2,650	1,490	2 4
100	39	18	2,250	1,030	5 2
113	34	14	2,400	1,130	−0 5
222	68	45	2,350	1,540	12 5
227	36	23	2,250	1,480	13 0
229	73	43	1,550	860	16 0
246	55	33	2,100	1,272	3 0
Average	50 1	29 9	2,581	1,306	7 3

accord with the minute volume output studies of Lundsgaard (5) The degree of prolongation bears a definite relation to the clinical condition These patients were suffering from more severe cardiac

TABLE 7

The velocity of blood flow and its relation to other aspects of the circulation in patients with arteriosclerosis and with evidences of myocardial degeneration with fibrillation of the auricles

Date	Test number	Name	Diagnosis	Age	Surface area	Temperature	Respiration	Pulse	Arterial pressure Systolic	Arterial pressure Diastolic	Venous pressure	Injected	Vital capacity	Vital capacity per square meter	Circulation time	Circulation time per square meter
					sq m.	F			mm. Hg	mm Hg	mm H2O	milli-curie	cc	cc	seconds	seconds
June 25	226	O C	Arteriosclerosis	71	1 64	n		124	96	44	47	6 7	3 000	1 820	23	14
February 27	113	W H	Myocardial degeneration	67	2 12	98 6	20	74	126	50	−0 5	3 8	2,400	1,130	29	14
February 10	74	R F	Myocardial degeneration	49	1 79	99 2	21	88	124	64	12	2 8	2 800	1,560	28	16
February 18	100	W H.	Myocardial degeneration	67	2 18	99 2	24	76	150	62	52	7 5	2,250	1 030	39	18
February 15	90	W D	Myocardial degeneration	55	1 78	97 0	26	46	84	50	24	3 6	2 650	1,490	38	21
June 25	227	J U	Myocardial degeneration	49	1 52	n	—	130	130	60	13	8 4	2,250	1,480	36	23
									140	70						
February 10	76	T M	Myocardial degeneration	50	1 83	98 0	23	72	136	56	41	4 1	3 600	1,960	44	24
January 14	69	D M.	Myocardial degeneration	53	1 66	98 4	26	80	132	52	12	6 3	2,500	1 500	42	25
								90								
September 24	247	F B	Myocardial degeneration, arteriosclerosis	65	1 60	97 6		64	126	64	−30	3 4	1,100	687	42	26 2
December 29	31	J W	Myocardial degeneration	43	1 68	96 6	20	58	104	52	12	2 4	3 150	1,870	47	28
December 4, 1925	23	J S	Arteriosclerosis, marked myocardial degeneration	73	1 87	97 6	21	48	148	72	70	2 0	3,100	1 650	55	29
September 1, 1925	15	J R.	Arteriosclerosis, myocardial degeneration	59	1 85				150	100		7 1	1,400	750	55	29
September 24	246	W D	Myocardial degeneration	55	1 65	98 1	n	42	94	65	30	7 8	2,100	1,272	55	33 3
December 16, 1925	30	J W	Myocardial degeneration	43	1 68	98 2	25	52	112	48	0 3	4 3	3 050	1,800	57	34
June 25	229	J W	Myocardial degeneration	45	1 75	n	24	112	88	78	16	6 4	1,550	860	73	43
June 23	222	J U	Myocardial degeneration	49	1 52	n	24	130	136	65	125	6 1	2,350	1,540	68	45

failure than patients with heart disease of similar etiology with regular rhythm The question therefore arises whether the severity of the cardiac failure in these patients is due to the abnormal rhythm, or whether the severity of the cardiac failure and the abnormal rhythm at least in certain patients are both expressions of grave myocardial damage As is well known, auricular fibrillation itself is not necessarily the cause of the clinical signs and symptoms of circulatory decompensation

The exact degree to which the abnormal rhythm and the myocardial lesion each contributes to the decompensatory state must vary from individual to individual Further studies are being attempted to investigate these factors more precisely

Examination of the circulation times of the two groups shows that the degree of retardation is less in those individuals who were without signs of congestive failure than in those patients who showed positive signs at the time of the test The average circulation time of patients with auricular fibrillation, but without signs of congestive failure, was 40 4 seconds or approximately 68 per cent above the extreme upper limit of normal, while it was 50 1 seconds or approximately 108 per cent above the extreme upper limit of normal in patients with these signs

II THE VELOCITY OF BLOOD FLOW AND ITS RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH ARTERIAL HYPERTENSION

Consideration of the dynamic factors concerned in the maintenance of arterial blood pressure shows that if the hypertensive state be due to a preponderant increase in cardiac energy, and the peripheral resistance be not proportionately increased, we might expect the velocity of blood flow to be increased If, however, the peripheral resistance is relatively more increased than the cardiac energy developed, and particularly if the elasticity of the vessels be diminished, we might expect that with the production of the hypertensive state, the velocity of blood flow would be lessened Were there an exact balance of these opposing factors the blood velocity would be unaltered Since factors such as cardiac energy, elasticity of the vessel walls, and peripheral resistance cannot be measured directly in man, the following study was undertaken in the hope that measurement of

the velocity of blood flow, which is a resultant of many complicated dynamic factors, might aid in our understanding of the mechanism of hypertension

The data obtained in studying patients with hypertension are divided into three groups (table 8) Group A consists of patients without any evidence of circulatory failure at rest at the time of the tests, and in whom the velocity of blood flow was normal Group B also includes patients who did not exhibit symptoms or signs of circulatory failure at rest or on exertion, but in whom there was definite slowing of blood flow Group C presents patients with decreased velocity of blood flow but with symptoms or signs of circulatory failure

The blood pressures of the patients of Group A, with one exception, at the time of test, varied from 160 mm Hg to 220 mm Hg systolic and from 76 mm Hg to 114 mm Hg diastolic. L S (no 96), whose blood pressure was normal, had suffered from dizziness and headaches for three years His physician had told him that his blood pressure was elevated and at the time of entry to the hospital the systolic blood pressure was 195 mm , the diastolic 50 mm The finding of signs of cardiac enlargement, in the absence of any signs of cardiac failure, suggested that the blood pressure of this patient had been elevated for some time The velocity of blood flow and the vital capacity were normal Were his blood pressure to fall without any diminution in the peripheral resistance the velocity of blood flow might be expected to become slowed That it did not become slowed suggests that his capillary resistance was due to functional causes rather than to persistent structural alteration such as widespread capillary occlusion due to arteriosclerosis E M (no 272) complained of breathlessness only on exertion, had never suffered from congestive failure, and his circulation was compensated at the time of test.

The presence of a normal velocity of blood flow in the patients of Group A is of considerable interest In no patients with hypertension did we find an increased velocity of flow This indicates that increased blood pressure, which in itself would tend to increase the speed of flow, is opposed by such factors as increased peripheral resistance

Group B consists of patients in whom there was a slowing of the blood flow, but who were able to continue their daily duties without

TABLE 8

The velocity of blood flow and its relation to other aspects of the circulation in patients with arterial hypertension

Date	Test number	Name	Diagnosis	Age	Surface area	Temperature	Respiration	Pulse	Arterial pressure: Systolic	Arterial pressure: Diastolic	Venous pressure	Injected	Vital capacity	Vital capacity per square meter	Circulation time	Circulation time per square meter
Group A	Patients with compensated circulation at time of test, whose velocity of blood flow was within normal limits															
					sq m	°F			mm Hg	mm Hg	mm H_2O	millicurie	cc	cc	seconds	seconds
November 6	307	B N	Hypertension	57	1 77	98 1		80	180	102	105	4 5	3,500	1,980	15	8 4
November 6	305	H M	Hypertension	70	1 74	98 1		90	194	104	200	7 0	2,700	1,552	18 5	10 6
February 10	80	D C	Essential hypertension	39	1 65	98 2	19	52	00	114	22	2 5			19	12
February 17	96	L S	Periodical hypertension	49	1 79	98 4	20	68	132	88	42	0 9	4,050	2,260	21	12
October 21	272	E M	Hypertension	46	1 81	98 2		82	184	110	80	5 0	3,800	2,099	22	12 1
January 12	56	B G	Hypertension	53	1 63	96 8	21	75	160	76	20	1 63	3,100	1,900	21	13
Group B	Patients with compensated circulation, whose velocity of blood flow was prolonged															
November 6	309	J M	Hypertension	57	1 79	98 6		58	205	104	85	4 0	3,650	2,039	26	14 5
November 6	308	M C	Hypertension	57	1 86	97 2		66	192	116	85	4 0	4,400	2,368	31	16 6
November 6	304	M S	Hypertension	61	1 76	98 2		76	190	112	65	4 0	2,900	1,648	30	17
June 16	198	J M	Hypertension	52	1 68	n	16	67	204	116	60	4 4			30	18
January 13	61	H B	Hypertension, auricular fibrillation	51	1 98	98 5	36	96	220	116	25	2 7	2,900	1,460	37	19

Group C Patients with decompensated circulation whose velocity of blood flow was prolonged

June 28	233	P S	Hypertension, auricular fibrillation	56	1 96	n	26	82	190	110	45	8 5	2,500	1 270	31	16
November 4	296	M B	Hypertension	50	1 60	98 4		94	214	110	135	4 5	4,100	2 560	29	18 4
October 26	278	J G	Hypertension	53	1 92	97 2		120 140	165	110	90	3 5	2 800	1 538	34	18 6
June 21	214	R. M	Arteriosclerosis, auricular fibrillation	61	1 64	n	19	104	220	134	40	4 0			31	19
November 5	300	M B	Hypertension	50	1 60	99 2		92	180	95	125	4 0	4,000	2,500	33	20 6
June 14	196	G H	Arteriosclerosis, hypertension auricular fibrillation	71	1 62	n	20	74	200	100	25	4 6	2,150	1,330	36	22
January 14	68	W H.	Arteriosclerosis, myocardial degeneration, hypertension, auricular fibrillation	50	1 87	97 8	26	38 45	190	95	—0 5	3 0	2,700	1 440	49	26

experiencing any symptoms of circulatory insufficiency We lay emphasis on these observations because they constitute the only instances in which we have encountered such prolongation in any group of patients without signs or symptoms of circulatory failure It is possible, that the abnormal increase in blood pressure constitutes a compensatory mechanism enabling the normal gaseous exchanges to take place in spite of the subnormal velocity of blood flow

Group C consists of patients in whom the slowing of the blood flow was associated with the symptoms or signs of circulatory failure This finding is in accord with our experience in patients with normal blood pressure suffering from circulatory failure The degree of slowing was approximately that observed in patients with cardio-vascular failure due to other causes In seven of the patients (nos 198, 296, 304, 305, 307, 308 and 309) the venous pressure was definitely above the extreme upper limit of normal, a phenomenon which has been observed by others (6) (7) (8)

The existence of two groups of patients with hypertension similar to our Groups A and B which cannot be differentiated clinically was also observed by Boas and Frant (9) They found that in one group the capillary pressures were normal, whereas in the other the capillary pressures were elevated Since we have not measured the capillary pressures of our patients we cannot state whether the two groups differentiated by Boas and Frant correspond to the two groups observed by us The fact that in none of the patients with hypertension did we observe increased velocity of blood flow suggests, perhaps, that the primary change in hypertension occurs in the peripheral blood vessels and that rise in the arterial tension is a secondary reaction on the part of the body aimed to maintain adequate blood supply to the tissues For, were the primary change the elevation of the blood pressure, one would expect to find a period when patients with hypertension show an increased velocity of blood flow This, however, has not been observed In some patients, on the contrary, the velocity of blood flow is retarded without clinical evidence of decompensation, and we suspect that in these patients the adjustment on the part of the heart to the opposed peripheral resistance was incomplete

SUMMARY

1 In this and the preceding (3) communication, eighty-seven measurements of the arm to arm circulation time by the radium C method, on male patients with cardiovascular diseases are presented, and an attempt is made to establish the relationship between the velocity of blood flow and other fundamental aspects of the circulation such as the vital capacity of the lungs, the venous and arterial pressures, and the cardiac rate and rhythm

2 The method as described in a preceding communication has been found adequate for the study of the various aspects of cardiovascular disease

The velocity of blood flow and its relation to other aspects of the circulation were studied in patients I With arteriosclerosis and with evidences of myocardial degeneration

1 Twenty-three measurements of the arm to arm velocity of blood flow and related aspects of the circulation were carried out on twenty patients who showed a regular cardiac rhythm

2 All these patients showed normal venous pressures, lowered vital capacities and circulation times that were slightly, moderately, or greatly prolonged, according to the degree of circulatory insufficiency

3 Sixteen measurements of the arm to arm velocity of blood flow and related aspects of the circulation in thirteen persons with fibrillation of the auricles showed that while the retardation of blood flow corresponded to the clinical evidences of cardiac decompensation, the prolongation of the circulation time was greater in proportion to the degree of circulatory decompensation than might be expected on the basis of our tests on similarly decompensated patients who showed a regular rhythm

II With Hypertension

1 Eighteen measurements of the arm to arm velocity of blood flow and related aspects of the circulation are presented on seventeen patients suffering from arterial hypertension

2 Patients with hypertension who exhibit no evidence of circulatory disability may be divided into two groups in one, the velocity

of blood flow is within the limits of normal, whereas in the other, the velocity of blood flow is retarded

3 In no patients with hypertension was an abnormally rapid velocity of blood flow observed

4 In seven patients without evidences of congestive failure, the venous pressures were found to be elevated

5 Patients with hypertension who show congestive failure have a retardation in the velocity of blood flow similar to that of patients with a corresponding degree of circulatory failure but with a normal blood pressure

CONCLUSIONS

1 Whereas the arm to arm circulation time in normal, resting, male individuals ranged from eleven to twenty-four seconds, it varied between eleven and seventy-three in male patients with compensated and uncompensated cardiovascular disease

2 The average arm to arm circulation time in fifty-three normal male individuals was eighteen seconds, whereas the average in eighty-six determinations in patients with cardiovascular disease was thirty-three seconds

3. The average arm to arm circulation time in those patients who showed no symptoms or signs of circulatory decompensation at the time of test averaged twenty-four seconds, whereas patients exhibiting symptoms or signs or cardiac failure showed an average arm to arm circulation time of thirty-eight seconds

4 The fact that the average circulation time in normal persons was eighteen seconds, and in patients with compensated cardiovascular disease, was twenty-four seconds, indicates that a retardation in the velocity of blood flow occurs in general before symptoms or signs become manifest

5 In general, the degree of cardiac decompensation at the time of the test was closely related to the degree of retardation of the velocity of blood flow

6 Prolonged circulation times always occurred in the presence of a failing circulation, except in one group of patients with arterial hypertension in whom a prolongation of the velocity of blood flow was observed, and who had never shown evidence of circulatory embarrassment

7 Patients with auricular fibrillation showed a disproportionate prolongation of the blood flow compared with patients with a similar degree of circulatory decompensation but with a regular rhythm

8 At the onset of circulatory failure, the retardation in the arm to arm velocity of blood flow appeared earlier than the increase in the venous pressure, and somewhat later than the reduction in the vital capacity In patients with improving circulatory function the venous pressure first returned to normal This was followed by a return of the velocity of blood flow to within the limits of normal, and somewhat later the vital capacity became normal

9 When the velocity of blood flow was measured several times in the same patient, it was found that the retardation of the velocity of flow preceded clinical evidence of increasing cardiac failure, and conversely, an increase in the velocity occurred before clinical evidence of improvement appeared

We wish to express our appreciation to Dr Francis W Peabody for his constant advice and encouragement

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APPENDIX

IA Abstracts of Histories and Physical Examinations of Patients with Arteriosclerosis and Evidences of Myocardial Degeneration with Regular Rhythm

215 D C entered the hospital complaining of dizziness Six days before entry he suffered what was evidently a cerebral hemorrhage with fainting, vomiting and vertigo Following this he had been somewhat disoriented until he entered the hospital During his stay in the hospital his neurological signs of cerebral hemorrhage improved Occasionally, on physical examination, auricular fibrillation was found Heart was not enlarged to percussion sounds were faint but of fair quality Discharge diagnosis—cerebral hemorrhage, arteriosclerosis, paroxysmal auricular fibrillation, chronic myocarditis

71 T H complained of dyspnea, orthopnea and congestive failure for 8 weeks He was cyanotic at time of admission P E (on admission)—heart was pushed to right and the rhythm was totally irregular There was fluid in both chests and thoracentesis was performed 3 times Patient received novarsurol and quinidin and became regular P E (time of test)—heart was regular and the circulation compensated No evidence of fluid observed Few moist râles at left base elicited Diagnosis—myocardial degeneration, arteriosclerosis

48 D M No cardiac history obtained Thickened radial and brachial arteries palpated Diagnosis—slight arteriosclerosis

17 E L had had no definite history of decompensation Sclerosed radial and brachial arteries were prominent The heart sounds were distant Diagnosis—moderate arteriosclerosis

63 J W complained of dyspnea P E (date of test)—distant heart sounds heard with rough systolic murmur over precordium, loudest over aortic area Moderate sclerosis of peripheral vessels was present Diagnosis—arteriosclerosis, myocardial degeneration

19, 20, 21 L C had had no history of decompensation The heart sounds were distant Moderately tortuous radial and brachial arteries palpated Diagnosis—moderate arteriosclerosis

57 J W had had increasing dyspnea for 3 years He suffered from diabetes for 4 years The heart was normal except for systolic murmur over precordium No history of congestive failure Beaded peripheral arteries felt Diagnosis—conspicuous arteriosclerosis, myocardial degeneration

58 J W had dyspnea and gastric and precordial distress for 3 years, congestive failure 2 months previously with nocturnal dyspnea Precordial pain was radiating to the left shoulder P E (at time of test) showed moderate cardiac enlargement The heart sounds were distant with rough systolic murmur over precordium which was loudest at 2nd right costal space Moist râles at both bases were heard. Conspicuous sclerosis of brachials radials and temporals were noted Diagnosis—myocardial degeneration, generalized arteriosclerosis

193 H. B had had no cardiac history He entered the hospital because of bleeding gums and perifollicular hemorrhages which were diagnosed as scurvy At time of test patient had improved and signs of scurvy had disappeared P.E showed distant heart sounds Size of heart was normal, sounds, regular There was conspicuous sclerosis of the femoral radial and temporal arteries Diagnosis—general arteriosclerosis

87 T O gave no history of cardiac decompensation P.E —size of the heart was normal, the sounds were inaudible Rough systolic murmur over the apex was heard All the palpable vessels were markedly sclerosed The thorax was fixed and the breath sounds were distant Diagnosis—arteriosclerosis , senile emphysema

199 A C complained of weakness loss of weight shortness of breath on exertion There was no dyspnea or orthopnea and no history of congestive failure P.E —size of the heart was normal, sounds were not heard Pulse was regular Conspicuous thickening and tortuosity of peripheral vessels was present The chest was barrel shaped and fixed The breath sounds were distant Diagnosis—generalized arteriosclerosis, myocardial degeneration, senile emphysema

223 H B suffered for several years from dyspnea on exertion, and from occasional precordial pain. One year ago he felt dizzy, had sharp precordial pain radiating to the left chest, palpitation sounds regular but distant The white blood cell count was 22 000 per cubic mm and therefore coronary thrombosis was suspected He was fairly comfortable until 4 weeks previous to present admission, when after a short walk he developed a rather sudden, marked sensation of suffocation He was relieved by nitroglycerine and was well except for short dyspnea On the day of admission after a walk, the sense of suffocation rather suddenly returned He vomited once He had a tight sensation over the upper chest, soreness but not pain and felt as if he were in extremis P E —Appeared to be "in extremis ", with marked dyspnea orthopnea and slight cyanosis Heart was slightly enlarged Sounds were distant, many crepitant râles at both bases No edema noted White blood cell count was 28,800 He improved gradually At time of test his circulation was compensated at rest no signs of congestive failure were noted though he was very weak and dyspneic on slight exertion Electrocardiogram showed signs of coronary occlusion. Diagnosis—coronary thrombosis arteriosclerosis

33 J O had had history of painful swollen right knee 37 years before admission. At time of admission he suffered from painful joints P.E —apex impulse

was not felt The left border of cardiac dullness was 9 cm Sounds were regular and of good quality Temporal arteries were tortuous, and the brachial and radial arteries were moderately sclerosed Diagnosis—infectious arthritis, arteriosclerosis

168 F S Following rest in bed for 8 weeks he became short of breath P E (at the time of test)—the heart size and sounds were normal There was flatness with suppressed breath sounds on left Râles at both bases were heart Pitting edema of legs was present Diagnosis—myocardial failure

242 J B suffered from periodic attacks of constriction of the chest with epigastric pain and vomiting P E —was negative except for marked arteriosclerosis He was observed in one attack during which the electrocardiogram showed complete ventricular asystole of about 11 seconds' duration After discharge from the hospital, patient showed almost daily attacks He was unconscious during attack He had no signs of congestive failure Diagnosis—Stokes-Adams syndrome, myocardial degeneration for 9 months

194 J W had had no history of cardiac decompensation P E —apex beat was not visible and not felt The left cardiac border dullness was in the 5th space, 9 cm The sounds were of good quality Rough systolic murmur with palpable thrill over aortic region was heard Brachial and radial arteries were hard, tortuous and beaded There was no edema of the ankles Diagnosis—generalized arteriosclerosis

29 R B gave no cardiac history P E (date of test)—Heart sounds were muffled Premature ventricular beats from different foci were shown by the electrocardiogram Cardiac impulse was not seen or felt Conspicuous sclerosis of the radial and brachial arteries was observed Diagnosis—general arteriosclerosis, myocardial degeneration

295 M C complained of weakness of 6 months' duration Frequently he was troubled by painful joints for 15 years Occasional palpitation with precordial pain was felt for several years which was associated with dyspnea on exertion At time of test he was unable to walk more than 600 yards without conspicuous dyspnea There was no sign of congestive failure P E —showed marked emaciation Apex in 5th space was 9 cm from midsternal line The sounds were distant and regular There was slight tortuosity of peripheral arteries Diagnosis—myocardial degeneration, syphilis

241 D M felt tiredness and shortness of breath on walking, for 2 years He gave no history of congestive failure P E —the heart was normal in size The sounds were regular and distant Conspicuous thickening of the peripheral vessels was noted Diagnosis—generalized arteriosclerosis, marked

36 J G complained of weakness, shortness of breath, and chronic cough of several months' duration P E —there was slight orthopnea. The heart was apparently normal The arteries were sclerosed Persistent moist râles at bases were heard Diagnosis—myocardial degeneration, emphysema

284 J G entered the hospital because of dyspnea, anorexia, and weakness beginning 4 weeks previously, when he developed severe attacks of nocturnal

dyspnea associated with a sense of pressure over the epigastrium P.E —There was orthopnea. The sounds were faint. A soft systolic murmur over the aortic area was heard Brachial and radial arteries were sclerosed Moist râles over both bases were heard The liver edge was palpable and tender Slight pitting edema over both ankles was present Diagnosis—arteriosclerosis, cardiac asthma

290 N L gave no history of congestive failure P.E.—the heart was normal in size The sounds were of good quality and regular in rhythm. Arteries were tortuous and thickened Diagnosis—arteriosclerosis

IB Abstracts of Histories and Physical Examinations of Patients with Arteriosclerosis and Evidences of Myocardial Degeneration with Fibrillation of the Auricles

226 O G gave no cardiac history and had never experienced shortness of breath P E —showed the heart moderately enlarged, the sounds rapid and distant and totally irregular in rhythm The lungs were hyperresonant and expansion was diminished Marked thickening of all palpable arteries was present Both legs were amputated from the thigh Diagnosis—arteriosclerosis, auricular fibrillation, myocardial degeneration

100, 113 W H gave a history of cardiac failure of one year with marked orthopnea and dyspnea At time of test he showed orthopnea and dyspnea. P E —Left border of cardiac dullness was 13 cm from the midsternal line The heart sounds were distant and totally irregular There was no pulse deficit Both bases were flat Moist râles were heard over the lungs Pitting edema of wrist, arms and legs was present Diagnosis—myocardial degeneration, auricular fibrillation

74 R F had had occasional shortness of breath with attacks of pain over pre cordium radiating to the left shoulder, arm and hand The pain was never sharp but rather dull and numb Slight dyspnea on exertion had been present during the previous few weeks P.E —showed the left border of cardiac dullness 12 5 cm from the midsternal line, sounds of good quality, and no murmurs Blood pressure (on entry) was 190 systolic and 100 diastolic No evidence was present of congestive failure Diagnosis—auricular fibrillation

90 246 R F five years ago, following an operation had shortness of breath, slight orthopnea, and swelling of legs and abdomen Diagnosis at that time was auricular fibrillation chronic myocarditis, coronary sclerosis and ascites He improved under digitalis and was able to work. Two days before admission he became dyspneic and orthopneic. Legs and abdomen were not swollen P.E — The apex impulse was not felt The left border of cardiac dullness in 5th space was 13 cm from the midsternal line Systolic murmur was heard over precordium, totally irregular rhythm was present with the apex rate, 80 radial rate, 72 Bubbling râles were heard over both bases at time of Test 90 Nails were slightly cyanotic. His circulation was compensated a rough systolic murmur was heard over the precordium Patient was discharged from the hospital and was well

until a month before second admission and Test 246, when he experienced cough and dyspnea One week before this 2nd admission he noted swelling of the ankles At time of Test 246 he had been completely digitalized and showed evidence of mild toxic effects such as vomiting P E was essentially the same as at previous test, except that he showed slight pitting edema over the ankles and of the subcutaneous tissues He was short of breath and unable to walk Liver edge was palpable and tender Diagnosis—myocardial degeneration, auricular fibrillation

222, 227 J U had had rapidly increasing marked dyspnea, soreness over epigastrium, cough, swelling of abdomen and legs of two months' duration P E showed orthopnea, dyspnea and cyanosis Veins of neck were distended The left border of cardiac dullness was 12 cm from the midsternal line Sounds were distant, rapid and totally irregular Arteries were soft The abdomen was large and the liver edge firm, 5 fingers below the costal margin There was pitting edema of the lower extremities and over the buttocks At the time of test the patient was still markedly decompensated with orthopnea, cyanosis and signs of congestive failure Hgb 100 per cent Diagnosis—myocardial degeneration, auricular fibrillation

76 T M had had fatigue for 1 year and dyspnea and paroxysmal palpitation for 3 months, orthopnea and nocturnal dyspnea for 2 months P E showed orthopnea with rapid breathing, the left border of cardiac dullness being 12 5 cm from the midsternal line, the heart rate 140, with a pulse deficit of 35 Sounds were weak and totally irregular, and a short blowing systolic murmur was present Both bases were dull Liver edge was felt 3 cm below right costal margin There was pitting edema of both ankles The circulation was compensated at time of test There was no edema The heart rate was 72 with no pulse deficit Slight pitting edema was present over buttocks Diagnosis—myocardial degeneration, auricular fibrillation

69 D M No history of congestive failure At time of test patient was in moderate distress P E showed the left border of cardiac dullness 12 cm from the midsternal line Systolic and early diastolic murmurs were heard over apex, with a loud first sound Rhythm was totally irregular The apex rate was 120, with a pulse deficit of 15 Diagnosis—mitral stenosis, auricular fibrillation

247 F B had dyspnea on moderate exertion and nocturnal, paroxysmal attacks of precordial distress associated with shortness of breath There was no history of congestive failure, P E showed heart apex impulse in the 5th space, 11 5 cm from the midsternal line Sounds were distant There was marked sclerosis of the peripheral vessels Diagnosis—myocardial degeneration, auricular fibrillation, arteriosclerosis, cardiac asthma

30, 31 J W had had shortness of breath and weakness, 8 months prior to admission, and precordial pain, orthopnea and nocturnal dyspnea There was no history of congestive failure Repeated electrocardiographic tracings showed spontaneous changes to normal rhythm, flutter and auricular fibrillation P.E at time of test showed the heart slightly enlarged, sounds of fair quality Radial,

brachial and temporal arteries were tortuous and thickened The circulation was compensated Diagnosis—myocardial degeneration, auricular fibrillation

23 J S had had increasing dyspnea for 3 years, orthopnea for 2 years On admission he showed marked cyanosis and general anasarca, and slight jaundice The vital capacity was 1350 cc. At time of test there were no signs of congestive failure except râles at both bases The left border of cardiac dullness was 17 cm from the midsternal line in the sixth interspace Absolute irregularity of ventricular rate was noted Systolic murmur was heard over apex The brachial and radial arteries were rigid Ronchi and râles were heard at both bases Diagnosis—general arteriosclerosis, chronic myocarditis, auricular fibrillation

II Abstracts of Histories and Physical Examinations of Patients with Hypertension

307 B M had had for 6 years dizziness and headaches but no symptoms of cardiac decompensation He had had arterial hypertension for at least 5 months P.E showed puffiness about both eyes The heart was enlarged to the left and a soft blowing systolic murmur was heard over apex. Lungs were clear Liver was not felt Blood pressure at first determination, 5 months previously, was 188 systolic, 90 diastolic Urine was negative Diagnosis—hypertension

305 H. M had had shortness of breath of 2 weeks' duration, and a choking sensation the night before admission. He had had several similar attacks during the previous 2 months but no symptoms of congestive failure There had been nocturia 2–3 of one month's duration P.E showed edema of conjunctivae and eyelids and the heart was moderately enlarged The sounds were regular and of fair quality No murmurs were heard There was no evidence of sclerosis The chest was fixed and flat Non tender liver edge was palpable two fingers below costal margin There was no orthopnea Urine showed no fixation of gravity, a slight trace of albumin There was no nitrogen retention, no signs of arteriosclerosis or congestive failure Diagnosis—hypertension

80 D C had had no history or signs of cardiac decompensation He entered because of accidental fall The systolic blood pressure of 240 was discovered accidentally 4 years ago The left border of cardiac dullness was 12 cm from the midsternal line Sounds were normal Diagnosis—hypertension

96 L S had had no signs or symptoms of decompensation and occasional headaches and dizziness for 3 years The blood pressure at entry was 195 systolic and 50 diastolic P.E showed the heart slightly enlarged, with the left border of cardiac dullness 12 cm from the midsternal line. A_2 was accentuated Peripheral arterial vessels were tortuous Diagnosis—arteriosclerosis, hypertension

272 E M had had attacks of dizziness, forcing him to lie down, associated with pain over the lower anterior chest and palpitation Patient was neurotic. There was no swelling of ankles or puffiness of face P.E showed tortuous retinal vessels, the left border of cardiac dullness 9.5 cm in the nipple line in the 5th space There was a slight systolic murmur over the tricuspid area in standing position The pulses were equal regular and synchronous, and the radial arteries neither

thickened nor sclerosed Lungs were normal Blood pressure during stay in hospital varied from 170 to 200 systolic and from 110 to 140 diastolic Urine showed a specific gravity of 1004, no fixation, slight trace of albumin, no sugar, numerous red cells 'Phthalein test of kidney function showed 57 per cent the first hour and 21 per cent the second hour Wassermann test was negative Diagnosis—hypertension, vascular nephritis

56 B G, for 2 years had been easily excitable, had occasional palpitation and shortness of breath for a few months He noticed occasional edema of the left ankle P E showed the left border of cardiac dullness 11 5 cm in the 5th space, heart sounds regular A_2 accentuated, and a soft systolic murmur over the precordium At the time of test the circulation was compensated Diagnosis—hypertension

309 J M had had dizziness of 7 months' duration but no dyspnea, orthopnea, or evidences of congestive failure Nocturia 3 had been present for 7 months P E showed the apex impulse in 5th space, 12 cm from the midsternal line The heart rate and rhythm were normal and no murmurs were heard Urine showed no fixation of specific gravity, very slight trace of albumin Diagnosis—hypertension

233 P S had had repeated attacks of shortness of breath with congestive failure during preceding 2 years, and breathlessness and swelling of ankles and legs of 3 weeks' duration P E on admission showed chest increased in anterior posterior diameter with numerous moist and musical râles heard anteriorly and posteriorly At time of test there was slight dyspnea and fluid in right chest Heart showed the left border of dullness well outside nipple line, no enlargement to right, action totally irregular, pulse deficit of 5 There was pitting edema of ankles and buttocks Diagnosis—myocardial decompensation (mild), general arteriosclerosis, auricular fibrillation, chronic myocarditis, pulmonary emphysema

308 M C had had precordial pain of several years' duration, with occasional palpitation Patient never stopped his work There was no dyspnea or orthopnea and no evidence of congestive failure P E showed heart apex in 5th space, 12 cm from the midsternal line, no murmurs, no thrills The lungs showed the signs of emphysema Liver was not felt Radial and brachial arteries were sclerosed and somewhat tortuous There were no signs of congestive failure Urine was entirely normal with no fixation of gravity Diagnosis—arteriosclerosis, hypertension

304 M S had no cardiac history but was troubled by dizziness and headaches Hypertension was discovered accidentally P E was entirely normal Urine was clear with no fixation of specific gravity There was nitrogen retention Diagnosis—hypertension

198 J M had been in good health and gave no history of weakness, dyspnea or congestive failure He came into hospital because of fainting for the first time P E showed the heart apex in 5th space and the left border of dullness 11 cm from the midsternal line Sounds were regular and normal There was slight thickening of brachial arteries Diagnosis—hypertension

296 300 M B, beginning 5 years before entry, had had attacks of pain in chest radiating to left arm, associated with dyspnea. Three weeks before entry, paroxysms of pain and dyspnea became more frequent and more severe Paroxysms lasted about 3 minutes and were agonizing P.E showed peripheral vessels sclerosed and tortuous, heart not enlarged No signs of congestive failure Urine showed slight trace of albumin and hyaline casts with a slight tendency toward fixation of specific gravity Diagnosis—hypertension, chronic nephritis

278 J G had had attacks of abdominal pain, and frequent attacks of severe nocturnal dyspnea, lasting 10 to 15 minutes Heart was normal in size, sounds regular and of good quality Faint systolic murmur was heard over the mitral area. Pulses were equal and of increased tension Liver edge was felt 3 fingers below the costal margin, moderately tender There was no edema over the extremities Urine showed a tendency toward fixation of specific gravity, slight trace of albumin, occasional hyaline and cellular cast There was no nitrogen retention. 'Phthalein output was 45 per cent in 2 hours Diagnosis—hypertension, vascular nephritis

214 R M for 6 weeks had had marked dyspnea and swelling of extremities P.E showed the heart markedly enlarged Sounds were loud, A_2 was accentuated Rhythm was totally irregular There was fluid in both chests and in the abdomen, and pitting edema over lower extremities Patient improved markedly under rest and digitalis and rhythm became regular spontaneously At time of test there were no signs of congestive failure His circulation was compensated at rest Hgb 70 per cent Diagnosis—hypertension, auricular fibrillation

61 H B had no history of congestive failure but had pain over left chest P.E at time of test showed diffuse pulsation over precordium, with the left border of cardiac dullness 11 5 cm in the 5th space Vessels were slightly sclerosed Diagnosis—hypertension, auricular fibrillation, myocardial degeneration

196 G H One week previous to admission ankles and knees began to swell and there was slight shortness of breath on exertion Patient was weak and unable to walk. P.E —heart was moderately enlarged, the second aortic sound was loud and ringing, and a loud, blowing systolic murmur replaced the first sound over the apex. Conspicuous thickening of radial, brachial and femoral arteries, and slight pitting edema of ankles was present Diagnosis—myocardial degeneration, arteriosclerosis, hypertension

68 W H had had dyspnea and attacks of precordial pain for 6 years, and orthopnea and bloody sputum for 2 months At time of test patient was in distress, orthopneic, and dyspneic, but had no edema or congestion of lungs Patient suffered from paroxysmal nocturnal dyspnea. P.E at time of test showed rapid breathing heaving cardiac impulse in the 6th space, 14 cm from the mid sternal line a systolic murmur with very loud booming first sound, and the aortic second sound ringing The rhythm was totally irregular, rate 70, no pulse deficit Urine was negative No nitrogen retention was present. Diagnosis—hypertension, auricular fibrillation

STUDIES ON THE VELOCITY OF BLOOD FLOW

V THE PHYSIOLOGICAL AND THE PATHOLOGICAL SIGNIFICANCE OF THE VELOCITY OF BLOOD FLOW[1]

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The velocity at which blood flows is of considerable consequence in maintaining physiological well being As has been pointed out in a preceding communication, it is not sufficient that an adequate amount of blood be expelled from the heart per minute, it is of primary importance that this blood be conveyed to the depots of utilization with the proper dispatch, and that it flow through the capillaries at sufficient speed to allow the proper interchange between blood and tissues It may be contended that whether an adequate volume of blood reaches the tissues through narrow arteries at a great velocity, or through large arteries at a lesser velocity is not of primary importance A given amount of blood ejected from the heart which might be entirely adequate if supplied through narrow vessels at a high velocity might, however, be inadequate if transported at a low velocity through wide vessels

We believe, therefore, that both the minute volume output and the velocity of blood flow are indices of two fundamental aspects of the circulation, aspects that are closely related, and which must both be satisfactory if the proper supply of blood to the tissues is to be maintained The relationship between volume flow and velocity flow through tubes of known diameter is a simple one and is expressed by the equation $V = \frac{A}{\pi r^2}$, where V = velocity expressed in seconds, A = volume per second, and r is the radius of the tube. It is evi-

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dent, therefore, that in a tube of constant cross sectional area, changes in the volume flow will be paralleled by changes in the velocity flow, and that any lack of proportionality must be due to alterations of the cross sectional area If in a given individual, simultaneous volume and velocity measurements were possible, their parallelism would provide important information on vasomotor and other changes in the functional cross sectional area of the vascular bed Further discussion of this interesting problem will be deferred until a later communication in which such measurements will be presented, and their significance discussed more fully

CONDITIONS WHICH AFFECT THE VELOCITY OF BLOOD FLOW

The fundamental characteristics in a hydraulic system which determine the velocity of flow are, of course, well known The mean velocity of a stream through a rigid tube is directly proportional to its cross sectional area and the difference in pressure from point to point The product of the cross sectional area multiplied by the pressure head, when divided by the coefficient of viscosity, gives the velocity of flow This has been expressed, according to Poiseuille's Law by the formula $\frac{(P_1 - P_2)r^2}{8\,LN}$ where $P_1 - P_2$ is equal to the difference in pressure, r is the radius of the tube, L is the length of the tube and N is the coefficient of viscosity Formulation of the factors by such a law is valuable in so far as it serves to focus attention on the character of the influences which determine velocity, but the futility of exact application of such a law to biological phenomena becomes at once apparent when one considers the constant flux of circumstances within the body The peripheral vascular bed is constantly varying, not only because of the delicate flexibility of the vasomotor arteriolar control, but also because, as Krogh has shown, certain capillaries may temporarily be entirely or partially closed It must, morever, be borne in mind that a certain change, such as peripheral vasodilatation, may influence the velocity of flow simultaneously in two and opposing directions The velocity of flow varies inversely as the resistance, and therefore vasodilatation, by lowering the resistance, tends to increase the velocity On the other hand, vasodilatation by increasing the cross sectional area of the flowing stream tends to

decrease the velocity This, and many more continually varying relationships, serve thoroughly to confuse theoretical formulations It is by such "vasomotor breezes," as Allbutt has termed them, that application of the abstract laws of theoretical physics is confounded, for, whether one or another factor predominates or, whether by chance they counterbalance, cannot be prophesied For the study of the velocity of blood flow within the animal organism, direct measurements must therefore be restorted to

THE PRINCIPLE OF THE METHOD UTILIZED ITS ADVANTAGES AND LIMITATIONS

By the velocity of flow is meant the time required for a certain length of the fluid column to pass a given point, or conversely, how long a certain cross section of fluid takes to flow a definite distance

The impossibility of securing such information along the brachial and pulmonary vessels during life is evident However difficult it may be to measure arteriolar and capillary lengths, and the length of venules, one can, nevertheless, accept the fact that from individual to individual, the path traversed by a given particle must be approximately uniform We have, therefore, as described in a preceding communication, measured the time necessary for the transportation of a minute amount of radium C through an arbitrarily chosen portion of the circulatory system, namely, from the antecubital vein of one arm to the antecubital artery of the other arm Only the pulmonary capillaries are traversed, and so the variability of the peripheral capillaries is largely, though not entirely, obviated The time required for the active deposit of radium to flow from the point of injection to the point of detection has been referred to as "the arm to arm circulation time"

In order that changes of the circulation time should be significant, it is of primary importance that under physiological conditions the path travelled should be uniform That the path traversed is uniform is attested to by a considerable body of evidence Our own measurements in over one hundred normal persons show agreement within a relatively small range. Repeated tests on the same individual at different times show close correspondence The work of Hering (1) on horses in 1828, the investigation of Vierordt (2) in 1858

on various small animals, and, more recently the work of G N Stewart (3) on dogs and cats, all these studies strongly support the conclusion that the path traversed is a uniform one

Although there is general uniformity of the path traversed, it must be recognized that, since one notes the time of the arrival of the first oncoming portion of the active deposit, the circulation time measured represents the velocity flow of the fastest particle through the shortest path That slight possible variations in the length of the larger vessels might alter the circulation time significantly is opposed by the findings of Hering (1), Vierordt (2), and more recently, Stewart (3) Hering found that the circulation time from the jugular vein of a horse to the tarsal vein required only several seconds more than the circulation time from the jugular vein to the other jugular vein The possible slight differences in length between the various precapillary or post-capillary vessels involved in the arm to arm pathway in man must therefore produce but an insignificant effect on the circulation time

One might contend that, although the circulation time would not be seriously affected by variation in the length of arterioles, arteries, venules, or veins, nevertheless it would be appreciably altered by changes in the number of available capillary pathways through the lungs Unfortunately, the question as to whether there is a significant vasomotor control of the pulmonary circulation is still in dispute Wiggers (4), in an excellent review of the question, concludes with Schafer that the fact that "the pulmonary system is provided with vasomotor nerves can no longer admit of doubt", but states that "provided the degree of lung inflation and heart rate remain unaltered, the vessels, that is to say, the arterioles, capillaries, and venules do not show any changes in size, nor is there any evidence of disappearance and reappearance of active capillaries" Wearn, Barr and German (5), on the other hand, by carefully cutting away the chest wall without injuring the parietal pleura of the cat, were able to observe the capillaries of the lungs without in any way manipulating the pulmonary tissue They found that the capillaries of the lungs exhibited spontaneous variation in calibre

Certain observations of G N Stewart (6), however, offer indirect evidence in this connection He states (p 27) "that the observed time of passage of the altered column of blood over an artery, when

salt or pigment solution is infused into the jugular vein, is in general not much longer than the time for which the infusion is kept up" This observation indicates that with animals under the experimental conditions of the study, there existed no partially closed capillaries For, if such existed, it would follow that they would offer greater resistance to the blood flow than other capillaries more widely open, and that the flow through them would be hindred so as to cause a tailing-out of the altered column of blood G N Stewart's observations would be in accord, however, with a situation in which the capillaries were either widely open or completely contracted

Our own observations, in the course of measurements in which radium C was used, do not afford additional evidence, because once the time of arrival of radium C is noted, the effect remains continuously present In general, therefore, it must be stated that experimental evidence is still contradictory concerning the question of the vasomotor control of the pulmonary circulation It should be emphasized, however, that no matter how the issue may eventually be decided, the constancy of the findings obtained by us in the same persons on different days, indicates that such vasomotor effects, if present, are not of sufficient importance to alter the clinical or physiological significance of our results

A further objection to the use of the circulation time as an index of the mean velocity of blood flow is to be found in the argument that the method used measures, not the actual velocity, but rather the speed of flow of the more swiftly moving central portion of the blood stream The argument may seem to contain an element of plausibility, but further analysis of the theoretical and experimental evidence weighs heavily against this possibility In the first place, fluid flowing through a tube cannot be considered analogous to a piston moving in a cylinder In the case of a piston, the entire friction occurs between the piston and the cylinder, whereas in a fluid every portion of the fluid develops friction against every other portion of the fluid When one bears in mind that each smallest portion of the fluid is constantly subject to varying frictional forces, and is, therefore, undergoing corresponding variations in its velocities, and that this situation is altered by discontinuous pulsatile waves with outward expansion and inward vibratory rebound in the case of the arteries, and by variable respira

tory waves in the case of the veins, and when, furthermore, one considers the innumerable branchings, the impossibility of what is the centrally moving stream at one time remaining the centrally moving stream at all other times, becomes manifest This question has been fully discussed by G N Stewart (6)

Not only theoretical considerations, but practical experience weighs against the velocity of flow of the central stream being far greater than the velocity flow of the outer stream If the central stream velocity were far greater than the peripheral stream velocity, one would find that, following the injection of dyes into one vein, samples of blood obtained from another would show considerable "stringing out", because the dye carried in the central stream would appear relatively early, and would be followed only later by the dye carried in the more slowly moving peripheral stream This problem was also carefully studied by G N Stewart, who found that such "stringing out" was inconspicuous

By studying the pulmonary circulation time, the quantity of blood in the lungs, and the output of the heart in one and the same animal, G N Stewart was able to secure valuable evidence to show that circulation times determined by the injection method afford a reliable index of the mean velocity

"If V is the minute volume of the heart in cubic centimeters, T, the mean circulation time of the lungs or of the lesser circulation in seconds, and Q the average quantity of blood in the lungs in cubic centimeters, or in the lesser circulation at the time when V and T are measured, then $V = \frac{Q\,60}{T}$ Even if some deduction is made from V for possible overestimation of that quantity, Q still comes out so high that it is not possible to assume, as Tigerstedt has done, that methods depending on injection of salts or pigments into the circulation give much too low a value for T, owing to the 'hastening on' of a portion of the injected substance in the axial stream In a network of capillaries filled with blood corpuscles, it is not conceivable that the same particle of injected material should continue moving with the maximum velocity for more than a small fraction of the total circulation time, its path being necessarily an 'out and in' one If we were to increase T materially above the actually observed (corrected) time, Q would come out impossibly high "

Although, in our experience, considerable "stringing out" occurs in pathological conditions of the circulation, one cannot interpret this

as necessarily a result of the different velocities of the central and peripheral streams In measurements of the velocity of blood flow in patients with congestive failure, we found that the concentration of the first portion of the radioactive substance to arrive in the antecubital artery was considerably less than the concentration of radium active deposit in the first oncoming portion in normal persons The concentration of the radium C increased moreover relatively slowly after its initial appearance It was, therefore, necessary to increase slightly the amount of active deposit of radium injected In order to be certain that the first diluted portion of the oncoming head of active deposit had not escaped detection, we performed check measurements both by means of our own procedure and by means of the injection of fluorescein These results showed that the radium active deposit is detected in the arterial vessels about the elbow in patients with cardiovascular disease as it is in normal persons The common clinical observation that the signs of congestion of the pulmonary circulation appear first at the bases of the lungs suggests that the "stringing out" effect observed in circulatory insufficiency may well be due to the fact that some of the blood flows rapidly through the upper, relatively normal, portions of the lungs, whereas other portions of the radium C which appear later are carried by the blood through other, more congested portions Drinker, Churchill and Ferry (7), in a recent study of the volume of blood in the heart and lungs, observed a similar condition They state

"One may assume that under rapid rates of blood flow all of the pulmonary capillaries are conducting blood and that the rate of movement in individual capillaries approaches equality, but that as blood flow into the right ventricle falls off the easiest routes are chosen, and with exceedingly low blood flow, many capillaries contain blood which is practically not in motion or which is moved slowly into the pulmonary veins "

Another source of variation in the circulatory system which might lead to slight differences in the circulation time has been noted by several observers, and was first discussed by Vierordt (2) He states

"If the first portion of the solution reaches the right auricle towards the end of diastole, it will meet blood which has flowed from the place of injection to the heart before the injection was made The next ventricular systole therefore dis

charges the blood containing the solution as well as the blood that has flowed just previous to the injection, and so the circulation time may be shortened by almost as much as the time required for a single systole A similar situation may arise in the left heart The error will obviously be greater (*1*) when the first portion of the injection mass arrives in the auricle shortly before its next systole If this portion is small, then through dilution, it will not be detectible, if, however, it is larger it will make itself manifest (*2*) The more incompletely the chambers contract, and (*3*) the slower the heart rate the greater will the error tend to be "

But even with the ventricular rate as low as sixty per minute the error must be less than two seconds

Finally we wish to point out that, whatever objections may be made to the use of the circulation time as a measure of the mean velocity of blood flow, these objections cannot impair the clinical significance of such observations for comparative purposes

THE RELATION BETWEEN THE ARM-TO-ARM CIRCULATION TIME, THE VITAL CAPACITY AND THE VENOUS PRESSURE

Examination of the results of our studies on the relation of the clinical observations to the measurements of the dynamic aspects of the circulation in patients with cardiovascular disease shows that while the rise of pressure in the antecubital vein measured according to the method of Moritz and Tabora is proportional to the degree of congestive failure, the rise above the upper limit of normal does not occur until relatively late in the decompensatory process Excluding all possible local causes, we have found that the rise in venous pressure is preceded by a definite period when the vital capacity is reduced and the velocity of blood flow is lessened A study of the anatomical and physiological characteristics of the veins affords an explanation of this finding

The muscular elements in veins are few, and elastic fibres are scanty, so that the veins may be considered as easily collapsible, but inelastic tubes They are freely distensible, therefore, until the limits of their capacities are reached, but only when this limit is reached are they resistant to further stretching During the stage of increasing venous filling, added amounts of blood result in very small increases in pressure Once, however, the vessels are full of blood to the limits of

their capacities, these relatively inelastic tubes can expand no further, and any additional amounts of blood flowing into the veins will then result in a conspicuous rise in pressure This is graphically illustrated by figure 1

These facts, therefore, indicate that a stage of engorgement precedes an increase of pressure in the veins and only after the veins have become filled to the limits of capacity do additional amounts of blood cause a rise in pressure In normal resting persons the veins are not filled to their full capacity, and so they are partially collapsed Their cross sectional area is smaller than when they are fully distended

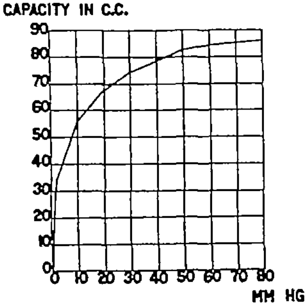

FIG 1 Curve of distensibility of a vein (by E H. Starling from figures given by Roy)

Since the velocity of flow is inversely proportional to the cross sectional area, a slowing of the velocity of blood flow would occur provided that the increase in the cross section of the blood stream were not counterbalanced by an increase in the pressure gradient within the veins Starling showed that the latter possibility is unlikely and our own results are also opposed to such a consideration The slowing of the blood flow in the veins during the period of increased venous engorgement might therefore be expected to precede, as in fact it does precede, the occurrence of increased venous pressure In all probability, similar events occur in the lungs and explain why the reduction in the velocity of blood flow occurs so early in circulatory failure That the

engorgement of the lungs leads to a diminution in their elasticity and so causes a limitation of the normal movements and a reduced vital capacity, has been suggested by previous observers (Von Basch, Siebeck, Peabody) With engorgement and distention of the pulmonary vessels, increase in the total cross sectional area of the blood stream through the lungs may well occur and lead to reduction in the velocity of blood flow

Consideration of the relation of filling to pressure and elasticity of the blood vessels suggests that this is at least one factor why the rise in peripheral venous pressure and appearance of edema in the lungs, are preceded by definite retardation in the velocity of blood flow, and by reduction in the vital capacity The question still remains, however, as to whether beginning congestive failure is signalled first by lessened velocity of blood flow, or by reduction in the vital capacity Although the sequence of events was not uniform in all types of cardiovascular disease, it may nevertheless be stated that the vital capacity was generally reduced first

Several explanations of this finding suggest themselves It is conceivable that the underlying, and as yet by no means clearly understood, mechanisms which are responsible for the lowered vital capacity may precede the mechanisms responsible for the slowing of the blood stream through the lungs Another possibility must be recognized, however The arm-to-arm circulation time, as tested by our method, measures the time required for the fastest particle of radioactive substance to travel from the point of injection in the antecubital vein to the opposite brachial artery The circulation time is therefore a somewhat simple expression of the blood flow in the arm as well as the blood flow in the lungs That the blood flow in the arms is extremely variable has been shown by previous observers (G N Stewart (8), Hewlett and Van Zwalwenburg (9)), and it is possible that these relatively great variations of blood flow in the arm may obscure variations of the blood flow in the lungs, which, while small, may nevertheless be an early and important indication of the beginning of circulatory failure Measurements of the pulmonary circulation time and of the pulmonary minute volume flow in man would be of considerable interest in this connection A third possible explanation exists and should be stated Clinical evidence, such as the appearance of moist râles first at the bases of the lungs, supports the possibility that passive congestion

may occur earliest, and perhaps exclusively, at the bases of the lungs If it appears while the circulation through the upper portions of the lungs is still normal, a reduced vital capacity may exist in the presence of normal pulmonary circulation time

Which of these possibilities is the true one cannot be established on the basis of the evidence now available, but studies are in progress to clarify the problem

SUMMARY

1 Evidence is presented that the arm to-arm circulation time in normal resting individuals is a measure of the mean velocity of blood flow

2 Our clinical measurements and the experimental evidence of others indicate that the path traversed by the radium C is uniform from patient to patient

3 With the onset of circulatory insufficiency, the vital capacity shows a decrease somewhat earlier than the velocity of blood flow, whereas the rise in venous pressure occurs only when the circulatory failure is considerably more pronounced

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ALTERATIONS IN LIVER FUNCTION AS AN INDEX OF TOXEMIA IN PNEUMOCOCCUS LOBAR PNEUMONIA

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Jaundice, varying from a slight icteric tinting of the sclerae to a pronounced generalized pigmentation of the skin and mucous membranes is not infrequently encountered during the course of lobar pneumonia Further, if examined for carefully, the presence of urobilin and urobilinogen in the urine is found to be practically constant during the acute febrile period of the disease Both jaundice and urobilinuria may be considered as probable indicators of liver damage, yet despite the fact their occurrence has long been appreciated, with the exception of the icterus index studies of Bernheim (1), the work of Kahler (2), and a few isolated case reports in the recent literature, there has been no detailed study of liver function in pneumonia Bernheim, in a study of the icterus index in various conditions, found it to be greater than normal in most of the cases of pneumonia studied Kahler, working with phenoltetrachlorphthalein, commented on the frequency with which high degrees of retention were observed in pneumonia. The lack of a detailed study of the liver function in pneumonia may probably be attributed in part to the lack of trustworthy methods for the clinical determination of liver function The comparatively recent introduction of the dye elimination tests and of the improved methods for the quantitative determination of circulating bile pigments has made it possible to carry on such a study Accordingly an investigation was undertaken in a series of cases of pneumococcus lobar pneumonia to determine (1) if pneumonia is uniformly attended with alterations in liver function, (2) if the various types of infecting pneumococci produce characteristic degrees of hepatic dysfunction, and (3) if there is any parallelism between the

degree of toxemia, as estimated by the clinical signs and ultimate outcome, and the amount of functional disturbance of the liver

The mechanism of liver damage in pneumonia is not clearly understood Among the recognized functions of the liver are the removal and rendering innocuous of circulating toxins and the temporary or permanent immobilization of circulating organisms Such toxins and organisms are presumably present in pneumonia As an additional factor in the causation of liver damage in pneumonia, Resnik and Keefer (3) have suggested the presence of anoxic anoxemia It is conceivable tht the liver may be damaged to an extent sufficient to be detected and measured by the improved functional tests now available

Various types of structural change in the liver have been described In the experimental pneumonias in monkeys, F G Blake and R L Cecil (4) found, as a rule, only cloudy swelling of the liver parenchyma This, too, is the usual type of change found in patients who have succumbed to the disease Acute catarrhal cholangeitis, actual inflammatory hepatitis, perihepatitis, cirrhosis, and fatty change have also been described as occurring during the course of acute lobar pneumonia Norris (5) cites the collected statistics of the hepatic complications of pneumonia as follows "Of 22,544 cases 373 or 1 65 per cent had jaundice, and of 344 so affected, 15 7 per cent died, of 173 patients, 20 23 per cent had a palpable liver, in seven of whom the liver was tender, of 201 patients, one had perihepatitis and one had liver abscess, of 3644, 19 (0 52 per cent) showed cirrhosis of the liver Of 144 autopsies, 5 55 per cent showed nutmeg liver, of 517 autopsies, 5 9 per cent showed fatty liver, of 239 autopsies, 5 29 per cent had acute parenchymatous hepatitis, of 400 autopsies 2 had jaundice, of 127 autopsies, 1 5 per cent had cholecystitis

PLAN OF STUDY

Liver function tests were performed on all definite cases of pneumococcus lobar pneumonia which were admitted to the Infectious Disease Pavilion of the New Haven Hospital Patients below the age of thirteen, obviously senile patients, those with atypical signs, and those giving a history of chronic alcoholism were not included The estimation of the rate of disappearance of the intravenously-injected dye, phenoltetrachlorphthalein, according to the method of S M

Rosenthal (6), was first employed as a measure of liver function In the latter part of the study the dye bromsulphalein was used Functional tests were performed on all patients during the acute febrile period of the disease and, in many instances, again after convalescence had been established The amount of serum bilirubin was estimated according to the quantitative method of van den Bergh (7), and the presence of urobilinogen and urobilin in the urine spectroscopically and according to the method of Schlessinger (8)

Liver function tests were also carried out on a heterogeneous group of cases of infectious diseases as a control for the estimation of the effect on liver function of fever, infection, and toxemia when these were not due to the pneumococcus Similarly a small group of cases of pulmonary tuberculosis were studied to serve as a control for the effect on liver function of pulmonary damage due to causes other than the pneumococcus

DESCRIPTION OF METHODS

Phenoltetrachlorphthalein test With a few minor variations, the technic described by Rosenthal was followed for the performance of the phenoltetrachlor phthalein test The test used is as follows 5 milligrams of the dye for each kilogram of body weight is given intravenously with from 40 to 50 cc. of physiologic sodium chloride The solution is first prepared by making a dilution of phenol tetrachlorphthalein in saline so that each cubic centimeter of the solution is equivalent to either 6 or 8 mgm. of the dye depending on the weight of the patient. The necessary amount of this solution is then injected into one of the large veins of the arm by means of a carefully graduated 50 cc syringe A 4- or 5-cc sample of blood is taken one hour after the injection. The blood is withdrawn with a different syringe from the vein of the opposite arm to obviate the possibility of contamination with any of the dye that might have adhered to the vein wall or to the syringe employed After the blood has coagulated the serum is separated from the cells by centrifugation and transferred to two 10 mm test tubes To one of these tubes which should contain approximately 0 8 cc. of serum, 0.2 cc. of a 5 per cent sodium hydroxide solution is added in order to produce an alkaline medium in which the purple color of the dye develops The concentration of the dye in the alkalinized serum is then determined by comparison with freshly prepared standards in a simple comparator and by direct sunlight. In order to compensate for the color of the serum, the tube containing unalkalinized serum is placed behind the standard on one side of the comparator and on the other side a tube containing distilled water is placed in front of the tube of alkalinized serum The figure obtained by the comparison represents the concentration of the dye retained in the blood serum at the time of withdrawal of blood

TABLE 1

Summary of clinical and functional findings in all cases studied

Patient	Type	Age	Day of disease	Lobes involved	Blood culture	Temperature	Pulse	Respiration	Leucocytes	Polymorphonuclears	End results	Dye retention	Urobilin	van den Bergh
										per cent		*per cent*		
1	IV	21	2	L L	Negative	104 5	120	30	29,000	89	Recovery	2	Faintly positive	Normal
2	I	21	5	R lung L U	Positive	104 0	120	40	25,000	91	Recovery	10	Positive	Normal
3	I	23	3	L L	Negative	103 0	110	36	22,000	88	Recovery	5	Positive	Normal
						98 6	70	18	8,000	70		Trace	Negative	
4	I	22	6	L L	Negative	103 0	104	36	15,200	86	Recovery	7	Positive	Normal
5	I	45	5	R L	Negative	102 0	105	30	17,000	89	Recovery	14	Positive	Normal
			21			101 0	90	24	3,300	64		Trace	Negative	
6	I	48	4	R L—L L	Negative	103 6	85	24	12,050	91	Recovery	9	Positive	Normal
7	I	40	5	R L—L L	Negative	104 0	120	30	28,000	96	Recovery	6	Positive	Normal
8	I	50	7	R lung	Positive	104 0	110	30	26,800	97	Death	55[b]	Positive	4 65
9	I	46	1	L L	Negative	105 0	120	28	19,950	83		4[b]	Negative	
			3		Negative	103 6	140	30	14,400	78	Death	8[b]	Positive	Normal
			6		Negative	102 0	130	38	33,000	92		12[b]	Positive	
10	I	34	5	R L	Negative	104 0	130	30	14,550	84	Recovery	11	Positive	Normal
11	I	26	5	R L—L L	Positive	105 0	120	55	23,500	89	Death	15	Positive	Normal
12	I	35	3	R L	Positive	102 6	130	30	9,600	71	Recovery	25[b]	—	—
13	I	43	4	R. M—R L	Positive	104 0	130	28	4,400	85		10[b]	—	—
			15	L L	Negative	100 0	80	24	15,600	82	Recovery	0		
14	I	25	4	L lung	Positive	103 0	120	40	20,860	81	Recovery	6[b]	—	—
			13		Negative				10,800	74		0		

15	II	21	7	R. U		102 0	140	70	41,320	96		20	Positive	
			11	L. lung	Negative	100 6	110	40	29 600	93	Recovery	8	Positive	Normal
			42			98 6	90	20	10,000	73		Trace	Negative	
16	II	35	3	R. U	Positive	105 0	132	30	22 000	90	Recovery	7	Positive	Normal
			17	R. M								0	Negative	
17	II	42	5	R. U—R. M	Positive	101 0	90	30	8 640	81	Death	3	Positive	Normal
18	III	62	4	R. U	Negative	104 0	120	35	15,000	81	Death	4	Faintly	Normal
				R M									Positive	
19	III	60	4	L. L	Negative	103 0	120	28	11 000	82	Death	7	Positive	Normal
20	III	40	5	R. L.—L L.	Positive	106 0	150	50	7 000	90	Death	9	Positive	Normal
21	III	50	3	R.L.—L. L	Negative	104 4	110	36	9,640	86	Death	8	Faintly positive	Normal
22	III	57	4	R. M—R. L.	Negative	104 0	100	26	19 850	88	Recovery	4[b]	Faintly positive	Normal
23	III	39	3	R L	Negative	103 6	110	35	21,400	92	Death	18[b]	Positive	Normal
24	III	60	6	L. lung	Positive	104 0	130	40	11,000	89	Death	32[b]	—	—
25	IV	27	2	R L—L L.	Positive	101 5	80	50	12 000	90	Recovery	5	Positive	Normal
			15		Negative	99 0	80	24	7,120	70		Trace	Negative	
26	IV	40	4	R M—R L	Negative	103 2	112	40	14 850	90	Recovery	17	Positive	Normal
			16		Negative	98 6	80	20	7,320	68		1	Negative	
27	IV	40	4	L. L	Positive	100 2	100	26	16,400	91	Recovery	38[b]	Positive	Normal
28	IV	62	3	R U—R M	Negative	104 0	110	35	19,000	90	Recovery	13	Positive	Normal
			11		Negative							5		
29	IV	45	4	R U	Negative	104 0	110	25	16,400	84	Recovery	12[b]	—	—
			16			99 4	90	20	8 200	75		5[b]		
30	IV	33	4	R L	Negative	103 0	120	34	11,700	84	Recovery	16[b]	—	—
			11			100 0	90	26				Trace	—	—

b = bromsulphalein in this and subsequent tables.

The standards are prepared as follows 10 mgm of phenoltetrachlorphthalein is added to 100 cc of distilled water This strength was suggested by Rosenthal as representing the approximate concentration that would be reached if all the injected dye remained in the plasma This solution is considered as representing a standard of 100 per cent and from this solution a series of standards is prepared in small uniform-sized 10-mm tubes ranging from 2 to 40 per cent To each tube one or two drops of 5 per cent sodium hydroxide solution is added in order to bring out the color

Bromsulphalein[1] *test* The technic first employed was similar to that described for the use of phenoltetrachlorphthalein with these exceptions 2 mgm of the dye per kilogram of body weight is the dosage employed, the drug is injected in 5 per cent solution, undiluted, the sample of blood is withdrawn 30 minutes after injection, and the 100 per cent standard is prepared by adding 4 mgm of bromsulphalein to 100 cc of water alkalinized with 0 25 cc of 10 per cent sodium hydroxide This technic was subsequently modified as follows The dosage was increased to 5 mgm per kilogram of body weight, the sample of blood was withdrawn 45 minutes after injection, and the 100 per cent standard was prepared by adding 10 mgm of bromsulphalein to 100 cc of water alkalinized with 0 25 cc of 10 per cent sodium hydroxide

Serum bilirubin The technic described by van den Bergh was followed in detail 0 5 cc of serum is precipitated with 1 cc of 95 per cent alcohol and centrifuged To 1 cc of the clear supernatant fluid is added 0 5 cc of 95 per cent alcohol and 0 25 cc of a freshly-prepared solution of Ehrlich's diazo reagent The color obtained is compared in a Duboscque colorimeter with a standard solution, and after accounting for dilution, the result is expressed in "units" Normal human blood serum contains 0 2 to 0 5 unit of bilirubin (i e , from 1 in 1,000,000 to 1 in 400,000)

Urobilin and urobilinogen No attempt was made to determine these substances separately

Spectroscopic method After first acidifying the urine with a small quantity of hydrochloric acid to make the spectrum more distinct, the urine is examined in the spectroscope Acid urobilin solutions, when very concentrated or in thick layers, absorb the entire blue end of the spectrum as far as the middle of the green On the other hand, a thin layer or a less concentrated solution shows an absorption between the green and the blue In contrast to urobilin the biliary pigments absorb the spectrum diffusely

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[1] The modified technic is based on a clinical study of the application of bromsulphalein as a test substance for liver function in which it was found that the employment of the larger dose of the dye facilitates the reading of the amount of dye retention when this is small and introduces no error if the sample of blood is withdrawn 45 minutes after the injection of the dye In a group of normal individuals, the blood serum was uniformly free of dye 45 minutes after injection in the dosage of 5 mgm per kilogram of body weight

Schlessinger's test The urine is rendered strongly alkaline with ammonia, filtered, and a few drops of a 10 per cent alcoholic solution of zinc chloride are added A beautiful green florescence occurs if urobilin is present

RESULTS OF STUDY

1 Are alterations in liver function uniformly present during the course of acute lobar pneumonia? In this series, dye retention not to exceed 2 per cent in one hour is considered normal An analysis of

TABLE 2

Liver function tests in pneumococcus pneumonia Types I and II

Patient	Age	Outcome	Day of disease			Type
			1–2	3–4	5–7	
			Per cent of dye retention			
9	46	Died 6th day	4[b]	8[b]	12[b]	I*
3	23	Recovered		5		I
14	25	Recovered		6[b]		I*
6	48	Recovered		9		I
13	43	Recovered		10[b]		I*
12	35	Recovered		25[b]		I*
7	40	Recovered			6	I
2	21	Recovered			10	I*
10	34	Recovered			11	I
5	45	Recovered			14	I
11	26	Died			15[b]	I*
4	22	Recovered			6	I
8	50	Died			55[b]	I*
16	35	Recovered		7		II*
17	42	Died		3		II*
15	21	Recovered			20	II

* Positive blood culture.

table 1 shows that only one patient (patient no 1) may be considered to have a normal functional test All of the remaining have a retention of the dye from 3 to 20 per cent in the cases where phenoltetrachlorphthalein was employed, and from 2 to 55 per cent with bromsulphalein The higher readings with bromsulphalein are to be expected, since comparative studies in known liver disease have shown that the retention of bromsulphalein in the blood serum 30 minutes after in-

jection is approximately twice that of phenoltetrachlorphthalein one hour after injection All cases, at some stage during the acute febrile period of the disease showed urobilin in the urine The serum bilirubin fell within normal limits in all cases except no 8 who had 4 65 units This patient had manifest generalized icterus, and showed 55 per cent retention of bromsulphalein In none of the others did there seem to be any relationship between the degree of dye retention

TABLE 3

Liver function tests in pneumococcus pneumonia Types III and IV

Patient	Age	Outcome	Day of disease: 1–2	3–4	5–7	Type
			Per cent of dye retention			
21	50	Died		8		III
23	39	Died		18[b]		III
22	57	Recovery		4[b]		III
18	62	Died		4		III
19	60	Died		7		III
20	40	Died			9	III*
24	60	Died			18[b]	III*
1	21	Recovery	2			IV
25	27	Recovery	5			IV*
28	62	Recovery		13		IV
29	45	Recovery		12[b]		IV
30	33	Recovery		16[b]		IV
26	40	Recovery		17		IV
27	40	Recovery		38[b]		IV*

* Positive blood culture

and the amount of bilirubin in the serum Patient no 1 who showed a retention of only 2 per cent of the dye was a very early case and might have shown evidence of dysfunction had another test been performed during the latter part of the acute febrile period When a second liver test was performed during convalescence, abnormal dye retention was never encountered, an indication of restoration of normal liver function

2 Do the various types of infecting pneumococci produce characteristic degrees of hepatic dysfunction? On analysis of tables 2 and 3,

in which the cases are arranged according to the type of infecting pneumococci and according to the day of the disease, in order to make conditions at least roughly comparable, no striking or characteristic differences among the various types can be detected with possible exception of Type IV pneumonia In all of the latter there is a greater degree of dye retention than in the other three groups during the third and fourth days of the disease

3 Is there any parallelism between the degree of functional disturbance of the liver and the degree of toxemia, as estimated by the clinical signs and the ultimate outcome? It will be seen from tables 2 and 3 that in pneumonias of Types I and III with one exception (table 2, patient 9) the greatest degree of retention was found in fatal cases In the Type II group no such relationship between retention and mortality appeared When judged from the standpoint of toxemia as manifested by clinical signs, and not considering the ultimate outcome, the degree of retention seemed to parallel the severity of the disease. The striking feature is that there was no evidence of greater disturbance in the Type III pneumonias with a high mortality rate than in the other types of pneumonia where the mortality rate was conspicuously lower It is evident also, from an analysis of the tables that the degree of dye retention tends to increase as the disease progresses, during the acute febrile period, the greater degrees of retention in each group occurring during the latter part of the first week

Control study Analysis of the results obtained in the heterogeneous group of infectious diseases indicates that typhoid fever, scarlet fever, and erysipelas may be accompanied by mild disturbances of liver function, minimal however, in comparison with that usually seen in the group of pneumococcus pneumonias Acute tonsillitis, though accompanied by high fever, showed no dye retention Although several of the patients in the tuberculosis group had extensive involvement of the lungs, impairment of the liver function was uniformly minimal or absent Only in the cases of tuberculous pleurisy with effusion was the amount of liver dysfunction comparable to that found in most of the cases of pneumonia. In all instances the tests were performed during the febrile period of the disease

TABLE 4

Infectious diseases

Patient	Age	Disease	Day of disease	Temperature	Pulse	Respiration	Brom sulphalein retention	Comment
							per cent	
F S	23	Scarlet fever	3	103 0	120	20	4	Patient moderately toxic No complications
			15	—	—	—	0	Recovered Mild serum sickness
S G	15	Scarlet fever	3	101 5	120	25	5	Patient moderately toxic No complications
			21	—	—	—	0	Convalescence completed
L M	29	Scarlet fever	2	100 8	100	20	5	Patient mildly toxic
R F	19	Scarlet fever	4	101 8	96	22	Trace	Toxicity very slight
D P	14	Erysipelas	4	102 0	128	24	0	Migratory erysipelas Patient moderately toxic
			15	—	—	—	0	Recovered
J K	64	Erysipelas	5	104 0	100	40	4	Facial erysipelas Patient slightly toxic
			13	—	—	—	Trace	Recovery complete
D S	60	Erysipelas	10	102 0	128	24	10	Facial erysipelas Patient mildly toxic Wassermann 4+ Chronic alcoholism
			16	—	—	—	6	Erysipelas process cleared
F T	24	Vincent's angina	7	99 2	92	20	0	Tonsillar lesions Toxicity slight
C R	30	Vincent's angina	10	101 0	110	24	Trace	Gingival lesions Moderate toxicity
E S	15	Tonsilitis	4	103 0	130	30	0	Patient appeared very sick
S C	17	Tonsillitis	2	103 0	85	22	0	Patient slightly toxic

H. P	43	Typhoid fever	21	103 8	96	28	12	Patient moderately toxic
			27	99 6	84	24	4	Patient much improved
			34	102 5	—	—	6	Mild relapse. Patient moderately toxic
			54	98 8	80	24	Trace	Patient afebrile for past 18 days
S L.	17	Pulmonary tuberculosis	—	104 2	122	26	4	X ray showed extensive involvement of both lungs
J M	54	Pulmonary tuberculosis	—	101 2	100	24	4	Extensive involvement of the upper two-thirds of both lungs
J K.	37	Pulmonary tuberculosis	—	99 6	104	24	5	X-ray showed extensive involvement of upper half of both lungs
P R	21	Pulmonary tuberculosis	—	103 0	96	24	4	Process moderately advanced bilateral
J C	35	Diabetes and tuberculosis	—	98 6	96	24	0	Involvement at right apex only
J Г	32	Tuberculous pleurisy with effusion	8/26	101 0	88	24	0	Moderate left pleural effusion
			9/12	—	—	—	12	Effusion considerably increased
			9/19	—	—	—	12	Effusion marked
			9/30	—	—	—	—	Chest tapped. *Artificial pneumothorax*
			10/2	—	—	—	—	Chest tapped Artificial pneumothorax
			10/24	—	—	—	5	Effusion slight
H F	60	Tuberculous pleurisy with effusion	11/20	102 4	90	26	—	Left pleural effusion—marked
			11/22	—	—	—	14	Temperature varied 100 to 103
			11/30	—	—	—	9	Fluid diminishing
			12/12	—	—	—	5	Fluid diminishing
			12/23	—	—	—	5	Slight amount of effusion

COMMENT

Although jaundice occurs relatively infrequently, the practically constant urobilinuria and the presence of dye retention indicate that the liver is uniformly affected during the acute febrile period of lobar pneumonia The results obtained in this investigation serve to strengthen the importance of the conception that pneumonia is not only a local disease attended by mechanical and chemical changes in the cardio-respiratory mechanism, but one attended by general toxemia which may affect the various systems of the body Degrees of liver dysfunction may be found which are comparable to those encountered in diseases such as cirrhosis of the liver and metastatic carcinoma of the liver

The degree of retention of the dye, in itself, affords no index of the toxemia and ultimate outcome It must be considered in conjunction with the type of infecting pneumococcus and the day of the disease on which the test was performed In general, a high retention early in the disease in Types I and III pneumonias may be considered as indicating severe toxemia, whereas its significance is considerably less in pneumonia caused by the Type IV pneumococcus There seems to be no relationship between the degree of dye retention and ultimate outcome in Type II pneumonia One cannot infer that the different functional results found in the various types of pneumonia are due to distinctive characteristics of the organisms themselves or to the toxins elaborated by them They may rather be due to differences in the individuals The most significant conclusion to be derived from the investigation is that retention of the dye is uniformly encountered during the acute febrile period of the disease

The results obtained in the control group of infectious diseases indicate that the function of the liver is more impaired in pneumonia than in some of the other types of infectious diseases Fever alone is not responsible for the liver damage as comparable elevations of temperature were present in some of the other disease groups without equivalent disturbances of liver function The presence of only minimal functional disturbances during the toxic period of scarlet fever suggests that if the disturbances of function encountered in pneumonia are due to circulating toxins, these toxins have a more

specific affinity for the liver Structural damage of the lung tissue, in itself, is not the important factor in the production of liver dysfunction, as evidenced by the normal findings even in the presence of advanced pulmonary tuberculosis The higher retentions in the presence of tuberculous pleural effusions are difficult to interpret. In both cases studied, removal of the effusion fluid was followed by moderate improvement of liver function

The factor of anoxic anoxemia could not be adequately studied in this investigation and further work along this line will be carried out. The cases where anoxic anoxemia is marked, e g streptococcus pneumonia and essential emphysema were not available during the period of this investigation

SUMMARY

In order to determine the effect of pneumococcus lobar pneumonia on hepatic function, dye elimination tests, serum bilirubin determinations, and urine urobilinogen and urobilin tests were performed on thirty patients, of which 13 were due to pneumococcus Type I, 3 to pneumococcus Type II, 7 to pneumococcus Type III, and 7 to pneumococcus Type IV Dye retention was found to occur consistently, the degree increasing as the disease progressed In considering the disease as a whole, no definite relationship between the severity of the infection (as measured by outcome) and the degree of liver dysfunction was found When considered according to the type of infecting pneumococcus, a suggestive relationship was found in the pneumonias of Types I and III Following recovery, dye retention was not present, indicating no permanent liver injury Urobilinuria was consistently present during the acute febrile period of the disease The serum bilirubin was within normal limits in all cases except one, a patient with manifest jaundice Impairment of function in the Type III pneumonias with a mortality of 87 per cent was not greater than in the Types I, II, and IV, with approximately 18 per cent mortality

An investigation of the liver function in a heterogeneous group of infectious diseases revealed either minimal alterations of liver function as contrasted with the group of pneumonias or none at all This is taken to indicate that fever or infection, in themselves are not sufficient to alter liver function markedly, rather that the changes found

ın the pneumococcus pneumonıas are probably due to an accompanyıng toxemıa whıch has a specıfic affinıty for the lıver No sıgnıficant alteratıons of lıver functıon were found ın cases of advanced pulmonary tuberculosıs, ındıcatıng that structural damage of the lungs ıs not alone responsıble for the changes found ın the group of pneumonıas

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THE EFFECT OF EPINEPHRIN ON THE PARTITION OF FOOD STUFFS IN OBESE AND NORMAL INDIVIDUALS

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In a recent report (1), we have shown that the characteristic rise in the total metabolism, pulmonary ventilation and pulse pressure, caused by the injection of a small amount of epinephrin,[1] is not significantly different in obese and normal individuals The respiratory quotient, on the other hand rises definitely less in the obese persons than in the normal subjects This difference suggests that the obese oxidize a relatively greater amount of fat after epinephrin injection than do normal individuals The interpretation of the respiratory quotient in terms of percentages of food stuffs burned, therefore, should throw some light on the metabolic processes of these two types, where the conditions of the experiment have been constant In this report we have endeavored to interpret these respiratory quotients in such manner and have also studied the effect of epinephrin injection on the partition of protein, fat and carbohydrate in obese and normal subjects The data from which the respiratory quotients were derived appeared in our previous paper (1), while new observations on protein metabolism are given below We will first consider the effect of epinephrin injection on protein metabolism as shown by study of the urinary nitrogen excretion

EFFECT OF EPINEPHRIN UPON PROTEIN METABOLISM

Since Blum (2) in 1901 first described glycosuria resulting from epinephrin injection many investigators have studied the action of epinephrin and have endeavored to interpret and explain its effect,

[1] The amount of epinephrin injected was 0 625 mgm of Parke, Davis and Company tablet "Adrenalin

not only upon carbohydrate metabolism, but also upon protein and fat metabolism. In a second paper (3) Blum found that glycosuria would eventually cease after repeated epinephrin injection, but also that it would reappear when olive oil was given. He believed this was due to the glycerin component of the olive oil, but he did not believe body protein was entirely spared in the production of the resulting glycosuria. This would presuppose an increased nitrogen excretion. Paton (4) agreed with Blum and reported an increased ammonia nitrogen excretion at the expense of the urea nitrogen, so that the total nitrogen excretion was not increased. This was emphatically denied by Underhill and Closson (5), who found no change in the distribution of nitrogen in the urine of their experimental animals before and after epinephrin injection. Eppinger, Falta and Rudinger (6) however, found that epinephrin caused an increased protein metabolism. Allen (7) reviewed and summarized the investigations of workers in this field and concluded that "Since there are so many negative results, adrenalin has no direct influence upon protein metabolism. The positive results may be explained by local tissue necrosis, fever, sweeping out of nitrogen by diuresis and possibly by formation of carbohydrate from protein."

Roubitschek (8) studied the same problem and believed that nitrogen excretion was increased only in those dogs having a positive nitrogen balance. In starving dogs there was no significant increase in the nitrogen excretion after epinephrin injection. The French investigators have gotten varying results. Brel (9) found no increase in nitrogen production in fasting and normally fed rabbits. Marie (10) reported an increase in blood urea after injecting epinephrin intravenously in rabbits, while Bru (11) found a characteristic increase of oxygen consumption, though no change was demonstrable in the nitrogen exchange after giving epinephrin subcutaneously to dogs. A temporary rise followed by a continuous high excretion of nitrogen on the day following epinephrin injection was reported by Allan, Dickson and Markowitz (12). Palladin and Tichwinskaja (13) varied the amount of epinephrin injection and found that 0.5 mgm given once daily caused no rise in the nitrogen output, while if the amount was increased, a rise in the total nitrogen and creatinin excretion followed. Lately Junkersdorf and Torok (14) have studied

the nitrogen metabolism as well as other factors in fasting dogs, before and after the injection of epinephrin, and they have reported an increase in the urinary nitrogen during the epinephrin period

From the above it can readily be seen that the results are somewhat conflicting In general, the work of Palladin and Tichwinskaja seems to offer the most satisfactory solution, for where an increased nitrogen excretion was found, the amount of epinephrin injected was usually in excess of 1 mgm On the other hand, in those cases where

TABLE 1

Total urinary nitrogen excretion

Name	Before epinephrin injection		After epinephrin injection					
	0 to 30 minutes	30 to 60 minutes	9 to 30 minutes	30 to 60 minutes	60 to 90 minutes	90 to 120 minutes	120 to 150 minutes	150 to 180 minutes
	mgm.	mgm.	mgm.	mgm	mgm	mgm	mgm	mgm
G O	423	538	411	420	417	544	166*	274*
M. K	172	133	202	121	135	122	116	111
M T	149	104	147	133	70	92	103	166†
A F	156	236	244	223	215	280	224	169
K. P	289	289	160	146	191	172	140	168
L J	143	287	246	268	215	223	210	176
Average	222	264	235	219	207	239	160	177

* Subject G O became nauseated during these two periods. He drank no more water during this time and his urine output dropped markedly This perhaps accounts for his low nitrogen excretion during these two periods.

† The urine output of subject M T was greatly increased during this period, probably accounting for the increased nitrogen excretion.

no increased output of nitrogen was demonstrable, the amount was generally less than 1 mgm

EXPERIMENTAL

The majority of the experiments upon the effect of epinephrin on protein metabolism have been carried out on dogs Therefore, to see if any such action existed in the normal human individual, six apparently well persons were given 0 625 mgm of epinephrin intramuscularly Each subject was studied in the resting, post absorptive

condition Urine collections were made at half hourly intervals and to assure a sufficient and constant quantity of urine during these short periods, the subjects were given a glass of water to drink at the beginning of each period For purposes of control, collections were made for two half hour periods before epinephrin was injected The results are tabulated in table 1

The average figures show no significant variation either before or after epinephrin injection, except during the last two periods, when other factors, such as nausea caused a diminution in the water intake The amount of urine excreted was therefore less and the total nitrogen output fell, probably because of the change in sweeping out of nitrogen from the tissues by lessened diuresis From our findings we may conclude that injections of small amounts of epinephrin have no significant influence upon protein metabolism

EFFECT OF EPINEPHRIN UPON FAT AND CARBOHYDRATE METABOLISM

In his monograph on metabolism, DuBois (15) states that, fourteen hours after his last meal, a normal individual derives approximately 15 per cent of his calories from protein This introduces an error of less than 1 per cent in the calculation of metabolism In order, therefore to interpret the respiratory quotients in terms of fat and carbohydrate burned, we have assumed that 15 per cent of the calories were obtained from protein Moreover, since the injection of epinephrin in the dosage employed produces no significant effect on protein metabolism, we have also assumed that 15 per cent of the calories were obtained from protein throughout the experiments The remaining 85 per cent of the calories were derived, therefore, from fat and carbohydrate With the aid of DuBois' chart (15) we have derived the per cent of fat and carbohydrate burned during the various periods before and after epinephrin injection The individual and average respiratory quotients of the obese and normal subjects are given in tables 2 and 3, and the average values of these respiratory quotients interpreted in the above manner are shown graphically in charts 1 and 2

On first glance at these charts, it will be seen that the obese subjects metabolize more fat than do the normal individuals during corresponding periods of time In the control periods, that is, before

the injection of epinephrin, the obese used up several times as much fat as carbohydrate, while the normal subjects burned up approximately equal amounts of each But during the first period after epinephrin was given, the obese subjects used only equal amounts of fat and carbohydrate, which condition was obtained in the normals during the preinjection period On the other hand, the normal sub-

TABLE 2

Respiratory quotients—obese subjects

Name	Basal		After epinephrin injection						
	1	2	10 minutes	20 minutes	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes
N C	0.79	0.75	0.81	0.79	0.85	0.81	0.78	0.77	0.74
L. V	0.70	0.72	0.83	0.78	0.80	0.76	0.73	0.71	0.73
H. C	0.75	0.78	0.80	0.78	0.78	0.79	0.74	0.75	0.71
M. P	0.88	0.79	0.88	0.85	0.81	0.76	0.81	0.88	0.82
M R	0.74	0.72	0.82	0.79	0.80		0.73	0.74	0.75
D A	0.81	0.81	0.92	0.81	0.77	0.83	0.76	0.78	0.80
R. P	0.77	0.75	0.79	0.75	0.82	0.74	0.72	0.70	0.73
Average	0.78	0.76	0.84	0.79	0.80	0.78	0.75	0.76	0.75

TABLE 3

Respiratory quotients—normal subjects

Name	Basal		After epinephrin injection						
	1	2	10 minutes	20 minutes	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes
J G	0.86	0.77	0.91	0.79	0.80	0.75	0.77		
J C	0.88	0.80	0.93	0.93	0.92	0.90	0.87	0.87	0.80
W B	0.76	0.87	1.01	0.95	0.88	0.81	0.80	0.84	0.84
H H	0.81	0.82	0.88	0.91	0.91	0.83	0.87	0.82	0.78
Average	0.83	0.82	0.93	0.89	0.88	0.82	0.83	0.84	0.81

jects metabolized 75 per cent of carbohydrate and only a minimal amount of fat at the end of the first 10 minute period The difference, thus, is quite striking In both the obese and normal subjects the comparative amounts of fat and carbohydrate used resumed the pre injection level at the end of 60 minutes

That epinephrin reduces the available glycogen supply in the liver

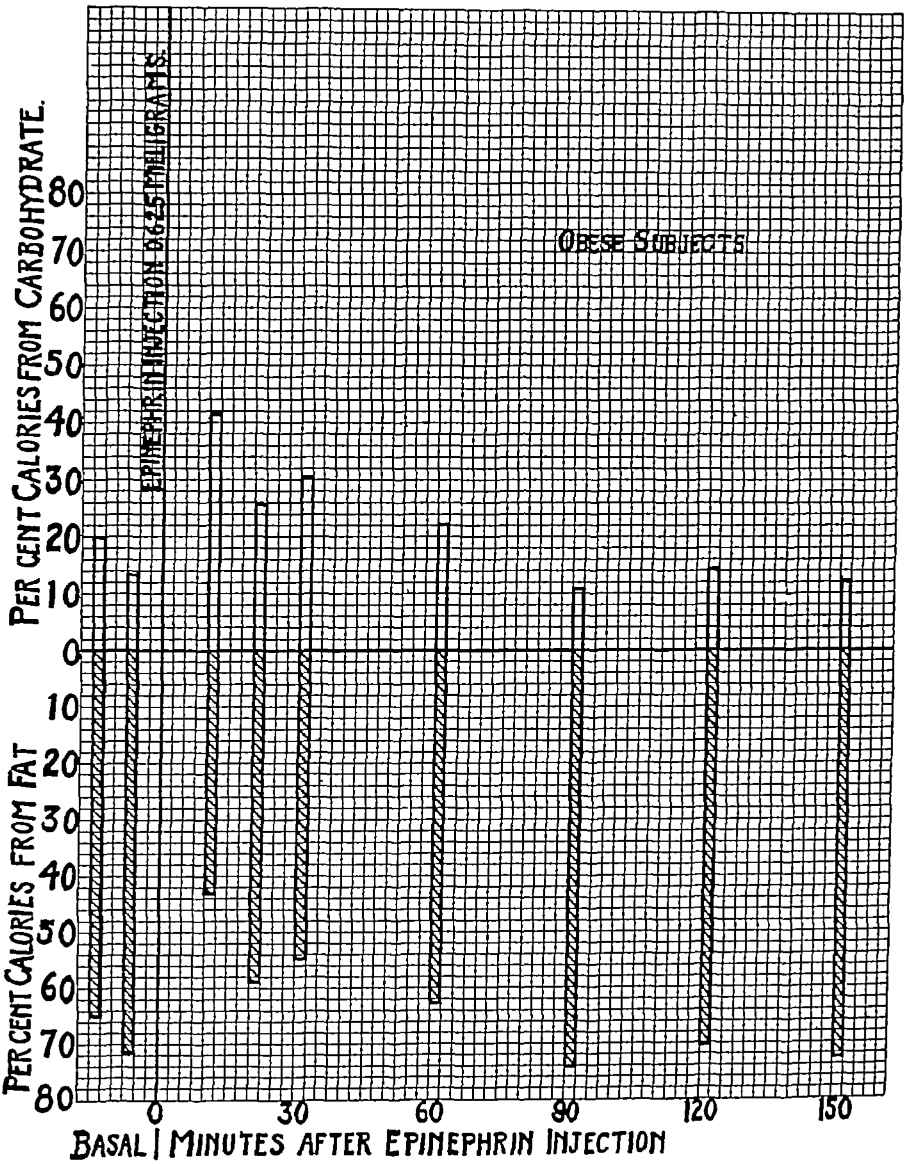

CHART 1 PER CENT CALORIES DERIVED FROM CARBOHYDRATE AND FAT AFTER EPINEPHRIN INJECTION—OBESE SUBJECTS

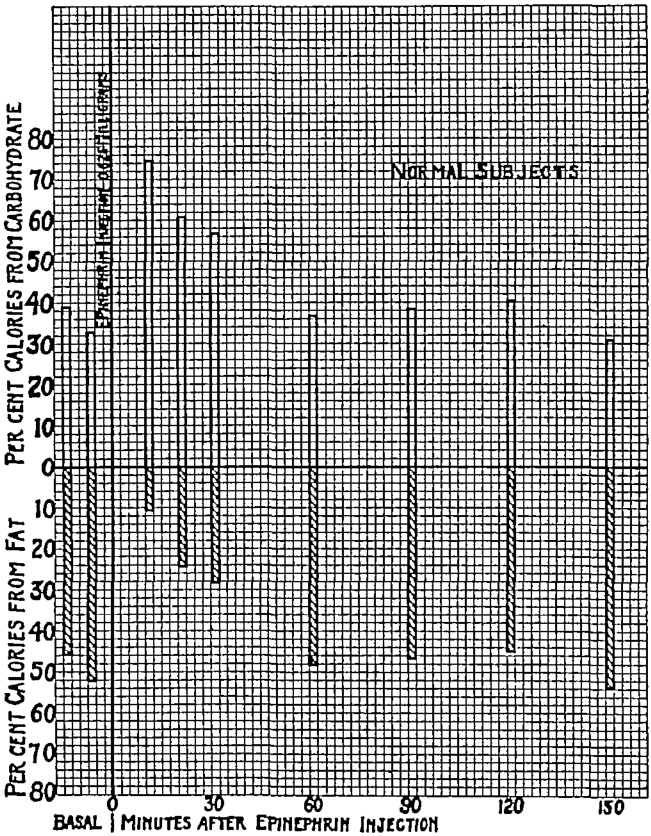

CHART 2 PER CENT CALORIES DERIVED FROM CARBOHYDRATE AND FAT AFTER EPINEPHRIN INJECTION—NORMAL SUBJECTS

is a well known fact (16) (17) (18) According to Geelmuyden (19) fat replaces the liver glycogen when this rapidly disappears as the result of some altered condition From our experiments, the obese individuals continuously metabolized more fat than carbohydrate, except during the 10-minute period following epinephrin injection, when equal amounts of each were used On the other hand, the normal subjects responded to epinephrin with an increased carbohydrate metabolism, which outbalanced the fat metabolism during the period of epinephrin effect Thus it would seem that the glycogen supply of the obese was limited when metabolism was stimulated by epinephrin Just what causes a decrease in glycogen storage and a corresponding increase in fat deposition in obese persons is not clear

CONCLUSIONS

1 The injection of 0 625 mgm of epinephrin produces no significant increase in protein metabolism in normal persons

2 Our experiments tend to show that obese individuals have less glycogen and more fat available for metabolism

3 When a metabolic stimulant, such as epinephrin is given, the most readily available food stuff is oxidized and in the case of the obese individuals, this is fat

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THE EXCRETION OF ALBUMIN AND GLOBULIN IN NEPHRITIS

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The present work was undertaken in order to ascertain whether the nature of the protein mixture excreted in the different types of nephritis is related to the type and severity of the disease

I HISTORICAL

A summary of the early literature on the relation of albumin to globulin ex cretion in the urine of nephritic patients has been given by Senator (1) and by Cloetta (2) A general survey of the literature has been given given more re cently by Geill (3) Hoffman was the first to take up the work in detail Using the early gravimetric methods in 1882 (4) he reported that any albumin globulin ratio may occur in any type of nephritis, and the value of the ratio is dependent not upon the type of change in the kidney, but on the intensity of the disease processes A low ratio signified a severe condition, a high ratio a mild one The ratio was found to rise with recovery in acute nephritis Lecorché and Talamon (5) found the ratio to decrease with increased severity of the disease Csatáry (6) found great fluctuations in the albumin globulin ratio, but made a general statement that he found ratios below 1 in cases of amyloid kidney and above 10 in cases of contracted kidney In severe cases the ratio fell. Cloetta (2) confirmed the work of Csatáry and reported low ratios in acute nephritis, with rise on recovery, and ratios usually over 10 in chronic nephritis He found no relation between the albumin globulin ratios in urine and in serum Joachim (7) reported a low ratio in amyloid kidney, a high ratio in contracted kidney A rise in the ratio signified a good prognosis while a fall signified a poor prog nosis Paton (8) reported albumin fractions high in chronic nephritis and low in acute cases He was unable to find high globulins in amyloid kidney, and was unable to form any conclusions on the relation of the urinary ratio to that of plasma Dreser (9) reported that the ratio has no diagnostic importance Gross (10) reported that the ratio varied and had no prognostic or diagnostic value Strauss (11) reported that the ratio had no diagnostic value, and that it was mostly so different from that of serum that one would be led to believe that the protein excretion is a selective process of the glomerulus Wallis (12) re

ported a low ratio in functional albuminuria and "leaky kidney," and a ratio of 6 in chronic and in toxic nephritis Autenrieth (13) found a distinct prognostic value in the albumin globulin ratio In agreement with Hoffman (4) he found ratios under 5 to the accompanied by a poor prognosis

The *relation of urinary protein excretion to plasma protein concentration* has been studied by a number of authors Kisch (14) showed that when the total protein excretion was less than 1 gram per liter the total plasma protein was over 7 per cent When the protein excretion increased, the plasma proteins fell below 7 per cent Linder, Lundsgaard and Van Slyke (15) found that when the protein excretion exceeded 1 gram per day there was a reduction of the total concentration of protein and of the albumin globulin ratio in the plasma, the plasma loss affecting chiefly the albumin Kollert and Starlinger (16) found that when the amount of protein excreted exceeded 1 gram per liter of urine the serum protein fell below 8 per cent, and continued to fall with increased excretion The serum albumin showed a progressive fall in the same manner, with increased protein excretion In the case of globulin, however, it was found that the higher the globulin fraction rose in the serum the higher the percentage of globulin in the proteins excreted in the urine, so that the albumin globulin ratio in the urine tended to decrease with the fall in the ratio in the serum

II METHOD FOR THE DETERMINATION OF PROTEINS IN URINE[1]

Albumin and globulin were separated by precipitating the latter with sodium sulfate, as in Howe's (17) technique for plasma protein separation The separated proteins were determined by the colorimetric method of Autenrieth (13, 18) which depends on the development of the biuret color by proteins treated with copper sulfate and alkali

The chief disadvantages of the Autenrieth method have been the lack of satisfactory standards, and the tedious technique of precipitating and washing the proteins We have found that standards may be prepared from solutions of pure biuret One milligram of Kahlbaum's biuret was found to give a color equal to that produced by 0 924 mgm of either albumin or total urinary protein This biuret equivalent of the proteins was obtained by comparison of Kjeldahl and colorimetric determinations on a number of urines Instead of precipitating with heat and acid we have precipitated the proteins with trichloracetic acid, and have centrifuged instead of washing on a filter

[1] A preliminary note on the method has been published in the *Proc Soc Exp Biol Med*, 1927, xxiv, 385

Magnesium sulfate was also tested for the precipitation of the globulins Saturation with magnesium sulfate was found to give a greater precipitation of protein than did 22 per cent sodium sulfate The presence of magnesium sulfate also decreases the depth of the color somewhat in the end reaction it was necessary to remove the magnesium by precipitating the albumin twice with trichloracetic acid

Since sodium sulfate gave a filtrate with a biuret equivalent of albumin equal to that of total protein, and since this same precipitant is used for the routine separation of the proteins in the plasma by Howe's method, we adopted sodium sulfate for precipitation of the urine globulins

Reagents

10 per cent trichloracetic acid solution

3 per cent sodium hydroxide solution

30 per cent sodium hydroxide solution

20 per cent copper sulfate solution, containing 20 grams $CuSO_4 \cdot 5H_2O$ per 100 cc solution

44 per cent sodium sulfate solution containing 44 grams anhydrous Na_2SO_4 per 100 cc solution This solution is saturated at 37° and must be kept at that temperature to prevent crystallization The sodium sulfate solution must be neutral to litmus

Standard biuret solution Dissolve 0 4000 gram of biuret in distilled water, and dilute to a volume of 150 cc. This solution will keep in the ice box at least a month

Preparation of urine samples Adjust a portion of urine (50 to 200 cc) to a pH of about 7 4, i e, slightly alkaline to sensitive litmus paper The reaction may be adjusted with more certainty by removing drops and testing with phenol red Filter if not perfectly clear This same specimen can now be used for the precipitation of globulin and for total protein

Total protein Measure 2 cc of the specimen into a graduated centrifuge tube, add an equal volume of 10 per cent trichloracetic acid, mix with a narrow glass rod, and centrifuge 5 minutes If the volume of precipitate is between 0 2 and 0 6 cc., the amount of protein in it can be read against the standard described below, and the analysis is continued as described in the next paragraph If the

volume of precipitate is larger or smaller, a second precipitation is performed, with enough urine to yield a precipitate of between 0 2 and 0 6 cc

Pour off the supernatant fluid, draining as dry as possible Dissolve the precipitate in about 3 cc of 3 per cent sodium hydroxide solution and wash into a 10 cc graduated cylinder with portions of the 3 per cent sodium hydroxide until the volume has reached about 9 cc Add 0 25 cc of 20 per cent copper sulfate solution, dilute to 10 cc with 3 per cent sodium hydroxide Mix thoroughly by shaking, let stand 10 minutes, centrifuge, and compare the supernatant fluid in a colorimeter against a standard prepared at the same time

To prepare the standard color solution measure 5 cc of the standard biuret solution, containing 13 33 mgm of biuret, equivalent to 12 3 mgm of protein, into a 10 cc graduated cylinder Add distilled water to 8 cc, add 1 cc of 30 per cent sodium hydroxide, 0 25 cc of 20 per cent copper sulfate solution, then dilute to 10 cc with water Mix thoroughly, let stand 10 minutes, centrifuge Transfer the supernatant fluid to the colorimeter cup, and compare with the solution of urine protein, setting the depth of the standard column at 15 mm

Calculation

$$\text{Grams protein per liter urine} = \frac{15}{R} \times \frac{12\ 3}{\text{cc urine used}}$$

$$= \frac{184\ 5}{R \times (\text{cc urine used})}$$

R being the depth of the protein solution matching 15 mm of the standard

Precipitation of globulin To 10 cc of urine prepared as described above, add 10 cc of 44 per cent sodium sulfate solution, mix well, and place in an incubator at 37°C for 3 hours Filter until a perfectly clear filtrate is obtained

Albumin With the filtrate from the sodium sulfate precipitation proceed as described under "total protein," performing the precipitation tentatively with a volume of filtrate equal to 4-fold that of the urine taken for total protein determination

Calculation

$$\text{Grams albumin per liter urine} = \frac{15}{R} \times \frac{12\ 3 \times 2}{\text{cc filtrate used}}$$

$$= \frac{369}{R \times (\text{cc. filtrate used})}$$

Globulin The globulin is estimated by difference

(Total protein) − (albumin) = (globulin)

The maximum error of the method is about ± 1 per cent for total protein and for albumin

Experiments on globulin precipitation

In order to determine the solubility of globulin in 22 per cent sodium sulfate, globulin was prepared from horse serum according to the

TABLE 1

Solubility of globulin in 22 per cent sodium sulfate solution

Solution number	Strength of globulin solution	Amount of protein in filtrate
	per cent	*per cent*
1	0 52	0 011
2	1 56	0 016

method described by Haslam (19) Two solutions were tested Solution 1 contained 0 52 per cent globulin Solution 2 contained 1.56 per cent globulin To each was added an equal volume of 44 per cent sodium sulfate, so that the precipitating mixture, contained 22 per cent of sodium sulfate The procedure was carried out as described in the method for urine The filtrate was analyzed for nitrogen by Kjeldahl The results are shown in table 1

From the results one may estimate that the amount of actual globulin in solution in the filtrate is 0 009 per cent, 0 002 per cent of impurity (presumably albumin) being dissolved in the filtrate when the 0 52 per cent globulin solution was precipitated, and 0 007 per cent when the 1 56 per cent solution was precipitated We have, however, not corrected our results for this solubility, as it is too small to affect their significance

To test whether the precipitation of globulin by 22 per cent sodium sulfate at 37°C is complete in 3 hours, comparative determinations were made, allowing the precipitating mixture to stand 3 hours and 24 hours Agreement was good, as is shown in table 2

TABLE 2

Effect of precipitation time at 37°C on globulin estimation

Determination number	Amount of globulin per liter	
	Incubation time	
	3 hours	24 hours
	grams	*grams*
1	3 8	3 6
2	2 6	2 6
3	2 4	2 4

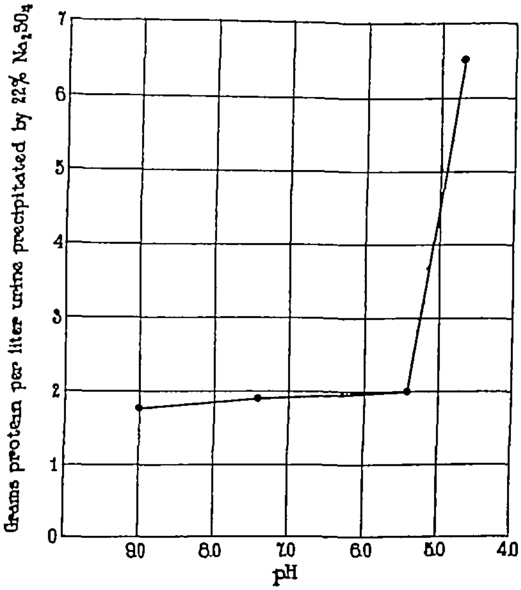

FIG 1 THE EFFECT OF pH OF URINE ON THE PRECIPITATION OF GLOBULIN

In order to test the optimum reaction for the precipitation of globulin with sodium sulfate, portions of urine were adjusted to pH 9, 7 4, 5 4, the isoelectric point of serum globulin, and 4 7, the iso-

electric point of serum albumin Figure 1 shows that between the isoelectric point of globulin and pH 9 0 the precipitation of protein is practically constant, while at the isoelectric point of albumin the amount of protein precipitated increases For this reason the acid urines were adjusted to the alkaline side of neutrality

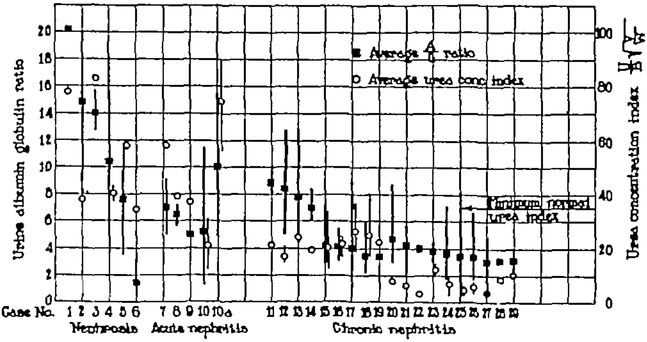

FIG 2 SUMMARY OF CASES CLASSIFIED ACCORDING TO URINE ALBUMIN GLOBULIN RATIOS AND UREA CONCENTRATION INDEX

For each patient a solid square indicates the average albumin globulin ratio during the observation period, the line running through the square indicates the extreme range of ratio found The open circle indicates the average urea concentration index, $\frac{U}{B}\sqrt{\frac{V}{W}}$, for a patient, the line running through the circle indicates the range of fluctuation of the index during the period of observation

III OBSERVATIONS IN NEPHRITIS

In a series of nephritic cases the *urinary proteins* were estimated by the above method The *plasma proteins* were estimated by the method of Howe (17) *Blood urea nitrogen* was estimated by the method of Van Slyke and Cullen (20) *Blood creatinine* was estimated by the method of Folin and Wu (21)

The urea concentration index was calculated from the urea content of blood and urine by a modification of the original method of Austin, Stillman, and Van Slyke The present index is calculated as $\frac{U}{B}\sqrt{\frac{V}{W}}$

and has been discussed in a previous publication (22) U = urine urea concentration B = blood urea concentration V = urine volume output in cc per hour W = body weight The index represents *the number of times the blood urea is concentrated in the urine when* $\frac{V}{W} = 1$, *or the volume output is 1 cc per hour per kilo* (e g , 60 cc per hour for a 60 kilo person), which is the average normal output When $\frac{V}{W} = 1$ the simple concentration ratio $\frac{U}{B}$ represents

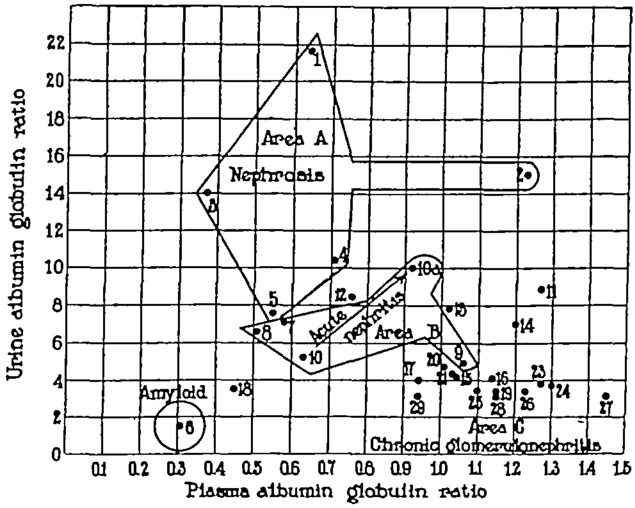

FIG 3 RELATION OF THE AVERAGE ALBUMIN-GLOBULIN RATIO OF URINE TO THAT OF BLOOD PLASMA

The numbers are those of the cases shown in table 4 The arrow between 10 and 10a indicates the direction of change in case 10 during recovery

the concentration index With a urine of greater volume, U is naturally less, and is multiplied by the empirical volume factor $\sqrt{\frac{V}{W}}$ in order to bring it up to the value it would have when $\frac{V}{W} = 1$

The results are shown in tables 3, 4, and 5, and figures 2 and 3 The types of nephritis are classified according to Volhard and Fahr as outlined by Linder, Lundsgaard, and Van Slyke (15)

The cases of nephrosis (tables 3 and 4 and figure 2) with one ex-

ception had high urine albumin globulin ratios, mostly above 10 The urea concentration index was normal or high in all these cases, and the blood urea nitrogen was below 0 20 gram per liter

Case no 6, figures 2 and 3 and table 4, with a urinary albumin globulin ratio of only 1 5 was not a pure nephrosis, but was complicated with pulmonary tuberculosis and amyloidosis It has been pointed out by other authors (6, 7, 23) that *amyloid degeneration* is associated with a high output of globulin, resulting in a low albumin globulin ratio in the urine. Csatáry (6) reported ratios below 1 Joachim (7) reported a ratio of 1 4 Gross (10) found ratios varying from 0.5 to 5 Our results showed a constantly low urinary albumin globulin ratio, ranging from 0.5 to 3 1, and averaging 1 5

TABLE 3

The albumin globulin ratio in the urine in different types of nephritis

Classification	Number of cases examined	Number having A G ratio above 10	Number having A G ratio between 5 and 10	Number having A G ratio below 5	Number having blood urea nitrogen below 0.20 gram per liter	Number having blood urea nitrogen above 0.20 gram per liter
Nephrosis	6	4	1	1*	6	0
Nephritis, acute	4	0	4	0	3	1
Nephritis, chronic	19	0	4	15	5	14

* Complicated with pulmonary tuberculosis and amyloidosis. See discussion.

The four cases of *acute nephritis* (tables 3 and 4 and figure 2) had urine albumin globulin ratios between 5 and 10 Only one case, no 10, was observed during the whole course of the disease, and the results of this case can be distinctly classed into two groups (tables 4 and 5 and figures 2 and 3) The early stage of the disease was characterized by an average urinary albumin globulin ratio of 5, and an average urea concentration index of 21 The period of recovery (10a, table 4, and figures 2 and 3) showed an average ratio of 10 and an average urea concentration index of 74 The blood urea nitrogen was at all times below 0 20 gram per liter The remaining cases observed had normal urea concentration indices and blood urea

Of the 19 cases of *chronic nephritis* observed, 4 had urinary albumin globulin ratios between 5 and 10, while 15 had ratios below 5 (tables 3 and 4, and figure 2) The ratios roughly paralleled the

Case number	Initials	Diagnosis	Age	Plasma proteins			Urine proteins average figures per 24 hours			
				Albumin	Globulin	A G	Albumin	Globulin	A G ratio	Number of estimations
			years	*per cent*	*per cent*		*grams*	*grams*		
1	W J	Nephrosis	27	1 65	2 21	0 75	15 1	0 7	21 6	2
2	G G	Nephrosis	24	2 40	2 04	1 18	7 5	0 5	14 9	3
3	B S	Nephrosis	12	1 02	2 75	0 37	4 2	0 3	14 0	4
4	M R	Nephrosis	29	1 83	2 50	0 73	13 5	1 3	10 4	6
5	B B	Nephrosis	23	1 46	2 47	0 59	9 9	1 3	7 6	8
6	G D	Nephrosis, amyloidosis, acute pulmonary tuberculosis	57	1 15	3 37	0 34	8 4	5 6	1 5	17
7	A C	Nephritis, acute	27	1 55	2 68	0 58	6 4	0 9	7 1	2
8	J My	Nephritis, acute	24	1 38	2 72	0 51	11 2	1 7	6 6	3
9	B Bl	Nephritis, acute	34	2 98	2 82	1 06	2 9	0 6	4 8	2
10	D G	Nephritis, acute	30	1 54	2 55	0 60	12 8	2 5	5 2	8
10a	D G	Nephritis, acute	30	2 45	2 75	0 89	7 0	0 7	10 0	6
11	R V	Nephritis, chronic	24	2 08	1 64	1 27	15 1	1 7	8 9	3
12	P L	Nephritis, chronic	28	1 98	2 61	0 76	5 0	0 6	8 4	3
13	M McC	Nephritis, chronic	20	2 01	3 23	0 62	3 9	0 5	7 8	3
14	E W	Nephritis, chronic	25	2 59	2 13	1 20	3 5	0 5	7 0	3
15	J L	Nephritis, chronic	16	2 05	1 96	1 04	6 7	1 6	4 2	9
16	R N	Nephritis, chronic	37	2 07	1 82	1 14	8 2	2 0	4 1	4
17	B F	Nephritis, chronic	24	1 77	2 08	0 85	3 2	0 8	4 0	8
18	S J	Nephritis, chronic	34	1 90	3 64	0 52	2 8	0 8	3 5	5
19	M G	Nephritis, chronic	12	2 85	2 57	1 03	1 4	0 4	3 5	2
20	E L	Nephritis, chronic	33	2 96	2 92	1 01	4 7	1 0	4 7	6
21	E Rt.	Nephritis, chronic	46	2 65	2 57	1 03	5 0	1 2	4 2	5
22	V S	Nephritis, chronic	27	—	—	—	4 8	1 2	4 0	2
23	S Ly	Nephritis, chronic	15	2 33	2 54	0 92	8 1	2 1	3 9	7
24	J C	Nephritis, chronic	27	3 24	2 41	1 34	7 8	2 1	3 7	16
25	R S	Nephritis, chronic	31	2 59	2 39	1 08	9 8	2 9	3 4	17
26	C A	Nephritis, chronic	34	3 48	2 89	1 20	4 4	1 3	3 4	12
27	M H A	Nephritis, chronic	20	3 09	2 31	1 34	5 0	1 6	3 1	7
28	H L	Nephritis, chronic	10	2 67	2 32	1 15	5 3	1 7	3 1	2
29	F M	Nephritis, chronic	13	2 62	2 79	0 94	3 4	1 1	3 1	4

* Values for the blood pressure and for the amount of edma and transudates are those fo[…] admission, except in case 24, in which there was a long hospital stay before the observations were[…] The findings have been recorded in this way in order to give as definite a picture as possible of the condition, before it had been modified by treatment

Average blood creatinine per 100 cc.	Blood pressure	Peripheral edema	Serous effusions	Duration of life after last observation	Remarks
mgm					
1 36	118/68	++	+	–	Seen 13 months later, very edematous
1 60	126/70	+	0	–	No worse 15 months later
1 15	110/76	++	++	–	Perfectly well 3 years later
1 53	120/78	++	0	–	No worse 19 months later
–	108/70	++	++	–	No worse 18 months later
–	110/70	++++	++	4 days	
1 58	146/88	++	++	–	Still edematous 16 months later Had lost ground
1 36	130/65	+	0	–	Not traced
1 57	160/92	+	++	–	Seemed recovered 15 months later
1 87	160/106	++	+++	–	Considerable improvement a year later
1 55	108/74	0	0	–	
1 59	148/76	+	0	–	Discharged unimproved 7 months later
1 84	164/90	+	0	–	Condition stationary 15 months later
1 62	166/98	++	0	9 months	Progress unfavorable. Died of diphtheria
2 01	150/92	++	±	6 months	Death probably from general septicemia
1 40	138/80	++	0	–	Seen 16 months later
					Kidney function worse but clinically better
1 64	138/92	++	+	17 months	Death from uremia and heart failure Autopsy
1 37	100/70	++	+	18 months	Death from uremia and asthenia
1 36	134/78	++	+++	11 months	Death from uremia and heart failure
1 31	120/60	+	0	–	Observed for 2 years. Progress unfavorable
6 10	270/120	++	+	1 month	Edema and hydrothorax relieved by digitalis. Death from cardiac decompensation
2 52	250/92	+++	±	7 months	Died in coma (from cerebral edema?)
24 73	206/126	0	0	3 days	Death from uremia
–	158/95	0	0	–	Free from symptoms 3 years later
16 60	190/130	+	0	21 days	Death from uremia
7 33	156/100	++	+	3 months	Death from uremia
5 20	225/114	Very slight	0	few weeks	
6 09	162/118	+++	++	2 months	Cardiac edema. Death from cardiac decompensation
–	120/90	+	+	6 months	Death from uremia
1 67	208/145	++	++	7 months	Died of pneumonia

he amount of peripheral edema exceeded a slight pitting it has been recorded in degrees, on a The record for transudates is similarly represented The symbol ± is used to record the light amount of dullness in the flanks or impairment of resonance at the lung bases when the

urea concentration indices in these cases, and the majority of cases with ratios under 5 had urea concentration indices under 15

TABLE 5

Case 10, acute nephritis, showing increase in albumin globulin ratio during period of recovery

Date	Urine				Blood plasma				Remarks
	Total protein excreted per 24 hours	Albumin excreted per 24 hours	Globulin excreted per 24 hours	Albumin globulin ratio	Total protein	Albumin	Globulin	Albumin globulin ratio	
1925	*grams*	*grams*	*grams*		*per cent*	*per cent*	*per cent*		
January 11	16 1	13 8	2 3	6 0	4 70	1 59	3 11	0 51	Period of apparently stationary condition
January 12	16 4	15 1	2 4	6 3					
January 19	20 7	16 4	4 3	3 8	3 65	1 30	2 35	0 55	
January 26	18 5	15 8	2 7	5 9					
February 1	20 1	16 1	4 0	4 0					
February 12	23 3	14 1	2 3	6 1					
February 24	7 3	6 0	1 3	4 6	4 09	1 54	2 55	0 60	Profuse diuresis began, with loss of edema and with general improvement
February 25	6 4	5 3	1 1	4 8					
Average				5 2				0 55	
March 29	10 3	9 1	1 2	7 6	5 19	2 45	2 75	0 89	Period of recovery
March 31	9 7	9 0	0 7	12 9					
April 8	8 8	7 4	1 4	5 3	5 29	2 36	2 93	0 81	
April 15	7 7	6 9	0 8	8 6					
April 28	4 9	4 5	0 4	11 2					
April 29	7 7	7 2	0 5	14 4					
Average				10 0				0 85	

The *correlation between excretion of protein in the urine and loss of protein in the blood plasma* is shown in table 6 and figure 3 From the point of view of total protein lost, table 6 shows a general decrease

of total plasma protein with increase in the total protein excretion when the averages of protein excretion from a number of cases are considered This finding is consistent with others in the literature, discussed previously

In attempting to correlate the albumin globulin ratio in the blood plasma with that in the urine, shown by figure 3, it can be said, in a general way, that the cases of nephrosis, area A, with high urine

TABLE 6

Relation of total protein in the urine to total protein in the blood plasma

Number of cases observed	Total protein		
	Plasma	Urine	
	Range	Range per 24 hours	Average per 24 hours
	per cent	*grams*	*grams*
1	6–7		5 3
11	5–6	1 6–12 0	5 8
10	4–5	1 3–16 1	8 6
7	3–4	3 3–16 3	9 8

TABLE 7

Relation between albumin globulin ratio in urine and duration of life

	Total number of cases	Number still living	Number dead	Remarks
Cases with average A G ratio exceeding 10	4	4	0	
Cases with average A G ratio between 5 and 10	9	6	2	One case untraced
Cases with average A G ratio under 5	16	3	13	Average duration of life in fatal cases 6 months

albumin globulin ratios, tend to have lower plasma ratios, while the cases of chronic nephritis, area C, with low urine ratios tend to have the higher plasma ratios the greater the proportion of albumin in the urinary protein loss the greater tends to be the albumin deficit in the blood plasma The cases of acute nephritis, area B, fall irregularly between areas A and C Case 10 shows the changes which occurred during recovery, from a low ratio in both urine and

plasma in the initial stages to higher ratios in the stage of recovery In this case the above general rule is reversed, urinary and plasma albumin globulin ratios showed a parallel instead of a reverse change Case 6, with nephrosis and amyloidosis, is also an exception The plasma and urine ratios are both lower than any others observed

The general tendency towards an inverse relation between plasma and urine ratios would seem to point to excretion of one type of protein in the urine as at least a partial explanation for the loss of that protein in the plasma In view of the deviations, however, it appears that other factors in addition to protein excretion are involved in the process of lowering the plasma proteins

An attempt was made to correlate changes in the amount of protein excretion with changes in the volume of urine excreted, by recording daily excretions, 12-hour excretions, and hourly excretions The results showed sometimes an increased protein excretion with increased volume, at other times no relationship, and, on a few occasions, the opposite effect

The prognostic significance of the albumin globulin ratio in the urine is shown in tables 4 and 7 Of the 4 cases with average ratios exceeding 10, one has recovered completely, while the remaining three show no signs of downward progress since the time of the original observations, which covers periods varying from 13 to 19 months (table 4)

Of the 9 cases whose average albumin globulin ratio in the urine fell between 5 and 10, two (nos 13 and 14) have died In both cases death was due to intercurrent infection, and cannot be ascribed to disease of the kidneys None of the cases in the group have developed serious impairment of kidney function

Of the 16 cases with average ratios under 5, 13 died within from 3 days to 18 months after the observations were made One of these cases (no 23) was seen a year later and had lost ground He is still living and free from symptoms 3 years after the observation The two remaining cases have been examined from time to time Both of these (nos 15 and 19) have shown a downward progress and kidney function is becoming progressively more impaired

Each tabulated urinary albumin globulin ratio is the average of estimations made on a number of different days The range of

values for the ratios found during the period of observation, as well as the averages, are shown in figure 2 The variations from day to day in the ratios of some of the cases were fairly large.

This variation and the consequent overlapping shown in figure 2 are sufficiently great to invalidate conclusions from any single determination The average of several days is required The variations appear due to actual fluctuations in the proportions of albumin and globulin excreted, and not to errors in technique

SUMMARY

The albumin and globulin in nephritic urines have been separated with Howe's sodium sulfate procedure, the separated proteins being determined by a modification of Autenrieth's colorimetric use of the biuret protein reaction A satisfactory standard for this method has been found in pure biuret

The albumin globulin ratio of the urine proteins was found usually above 10 in nephrosis, between 5 and 10 in acute nephritis, with a low ratio during the early stage followed by a higher ratio during recovery, usually below 5 in the advanced stages of chronic glomerular nephritis with urea retention and impaired kidney function In one case of amyloid nephrosis the ratio was very low, 1 5, in accord with the previous literature

The low ratios in advanced chronic nephritis were associated with low urea concentration indices and poor prognoses Of 15 cases observed with average urinary albumin globulin ratios below 5, all but 2 have died in less than 18 months, and these 2 have shown progressive decrease in renal function

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TABLE 1

Liquids of immersion, 10°C	Differences of weights in grams per 100 of muscle immersed after								
	2 hours	8 hours	17 hours	19 hours	24 hours	36 hours	43 hours	48 hours	72 hours
Chart I									
Plasma normal blood									
I A	−2 95				1 9	11 8			12 7
I B	−2 6				1 22	6 62			10 4
II A	−4 24				−1 56	3 29			9 0
III A	−7 94				−5 92	3 57			14 0
Nephritic Edema +++									
II B	−2 0				6 16	12 5			19 0
III B	−6 1				−0 88	10 0			15 0
IV A	−1 7				10 6	15 4			21 0
IV B	−2 8				8 86	14 7			16 9
Chart II									
Plasma normal blood									
V A		−4 9			−1 9				5 0
VI A	−2 8		2 3	2 2				7 4	8 1
VI B	−3 3		−1 2	−0 9				7 4	9 0
Cardiac Edema +++									
V B		−3 4			5 0				7 0
VII A	−5 9		−2 2	−2 0				9 4	12 3
VII B	−3 9		5 8	6 2				13 0	14 5
Chart III									
Iodine poisoning No edema									
VIII A	−2 3				4 1			12 7	14 9
VIII B	−2 4				2 0			11 7	13 0
IX A	−1 4				5 3			8 7	12 5
X A	−3 9				3 7			7 3	9 8
Cardiac decompensation Edema ++++									
IX B	−4 9				−2 6			6 6	10 6
X B	−1 2				6 7			11 0	15 7
Chart IV									
Cardiac decompensation Edema +++									
XI A	−6 9				−5 5			−3 8	4 2
XI B	−7 8				−7 26			−1 3	6 3
Cardiac decompensation Edema +									
XII A	−5 17				−1 15			1 38	1 9
XII B	−6 6				−4 6			−1 4	2 8

TABLE 1—*Continued*

Liquids of immersion 10°C.	Differences of weights in grams per 100 of muscle immersed, after—								
	2 hours	8 hours	17 hours	19 hours	24 hours	36 hours	43 hours	48 hours	72 hours
Chart V									
Iodine and CO poisoning No Edema									
XIII A	−2 9				6 6			8 5	13 5
XIII B	−1 8				1 26			8 4	11 8
XIV A	−1 5				4 3			7 8	9 7
XV A	−5 8				−4 9			0 9	5 8
Nephritic. Edema ++++									
XIV B	−5 64				−1 4			3 8	6 6
XV B	−6 3				−3 4			−1 4	3 3
Chart VI									
0.9 per cent sodium chloride									
XVI A.		−1 7			−5 8		−5 1		0
XVI B		−0 8			−0 4		4 4		11 0
XVII A.		−2 5			−4 9		−5 7		−4 5
XVIII A		−0 4			12 4		13 3		10 5
Mammalian Ringer's Solution									
XVII B		0 67			6 2		10 6		9 9
XVIII B		2 3			4 2		−3 3		0 4
XIX A		0 88			5 7		7 5		14 0
XIX B		0 6			5 8		9 3		15 4
Chart VII									
Frog Ringer's solution									
XX A		−2 2		−2 6				−2 1	−4 9
XX B		−2 2		−4 6				−4 4	−6 2
XXI A		0		5 1				9 6	11 8
XXII A.		−2 5		−3 5				−0 6	−2 5
0 45 per cent sodium chloride									
XXI B		14 4		25 2				22 6	22 6
XXII B		8 5		23 0				24 0	24 6
Chart VIII									
Distilled water									
XXIII A	37 0				73 0		58 0		36 0
XXIII B	39 0				65 0		55 0		35 0
XXIV A	34 0				64 0		53 0		34 0
XXIV B	28 0				65 0		50 0		30 0

TABLE 1—*Continued*

Liquids of immersion 10 C.	Differences of weights in grams per 100 of muscle immersed, after								
	2 hours	8 hours	17 hours	19 hours	24 hours	36 hours	43 hours	48 hours	72 hours
Chart IX									
Plasma normal blood									
XXV A	Muscles weighed, kept in				−4 6	−6 6			2 0
XXVI A	moist air bottles 24				15 6	7 3			6 6
XXVII A	hours, weighed again				−2 3	−4 0			0 8
Cardiac decompensation Edema	and then put into the								
+++	liquids of immersion								
XXV B					0	−1 7			7 8
XXVII B					−2 8	−4 6			7 3
0 9 per cent sodium chloride									
XXVI B					6 6	4 1			14 7
Chart X									
Pleuritic fluid (pneumonia)									
XXVIII A		−3 3					1 66		0 23
XXVIII B		−3 2					−0 53		2 6
XXIX A		−6 0					−1 23		2 3
XXX A		−2 46					−0 9		0 56
Chart XI									
Ascitic fluid (portal cirrhosis)									
XXXI A	−1 4						−1 5		0 27
XXXI B	−2 8						−2 5		0 31
XXXII A	−2 7						−1 8		1 4
XXXII B	−3 3						−4 0		1 0
XXXIII A	−2 0						−2 2		0 9
XXXIII B	−2 8						−3 7		1 3

of blood pH, and the plasma was kept covered by a layer of paraffin oil and at a temperature of 8° to 12°C In order to check our results we took two liquids of immersion at the same time, as, for example, plasma from a patient with no edema or condition commonly associated with edema, and plasma from a patient with severe edema Into portions of the plasma from the edematous subject we put both gastrocnemii of one frog, into the other plasma we immersed both muscles of a second frog We then took a third frog or a third and a

fourth frog and immersed one muscle of each in each of the two kinds of plasma By repeatedly immersing, drying and weighing the muscles of a frog, we found that we were able to perfect a technique which

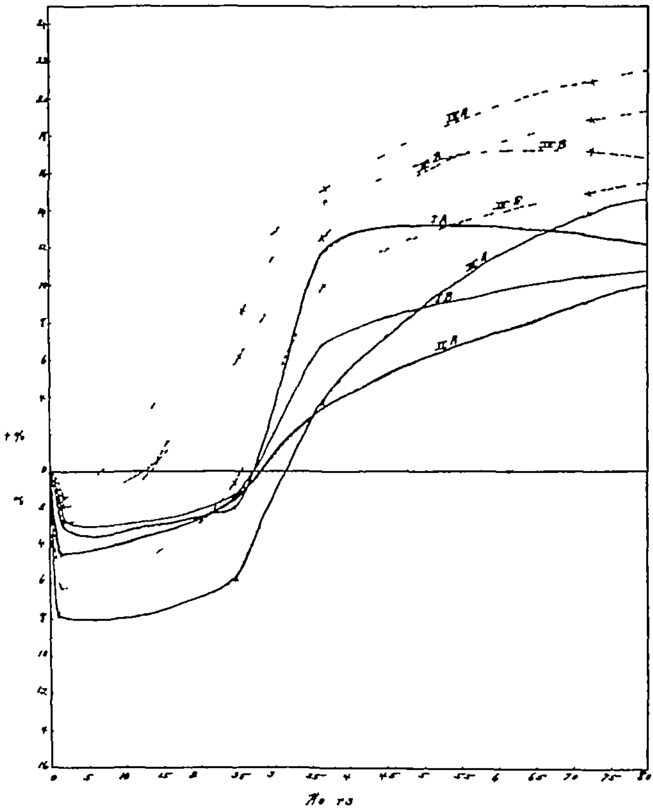

CHART I

——————— Plasma normal blood

-------------- Plasma from patient with nephritis and edema +++

The increase in weight is greatest in muscles A and B of frog VII which were placed in the plasma of a patient with severe edema on a cardiac basis The greatest initial loss of weight is also in one of these

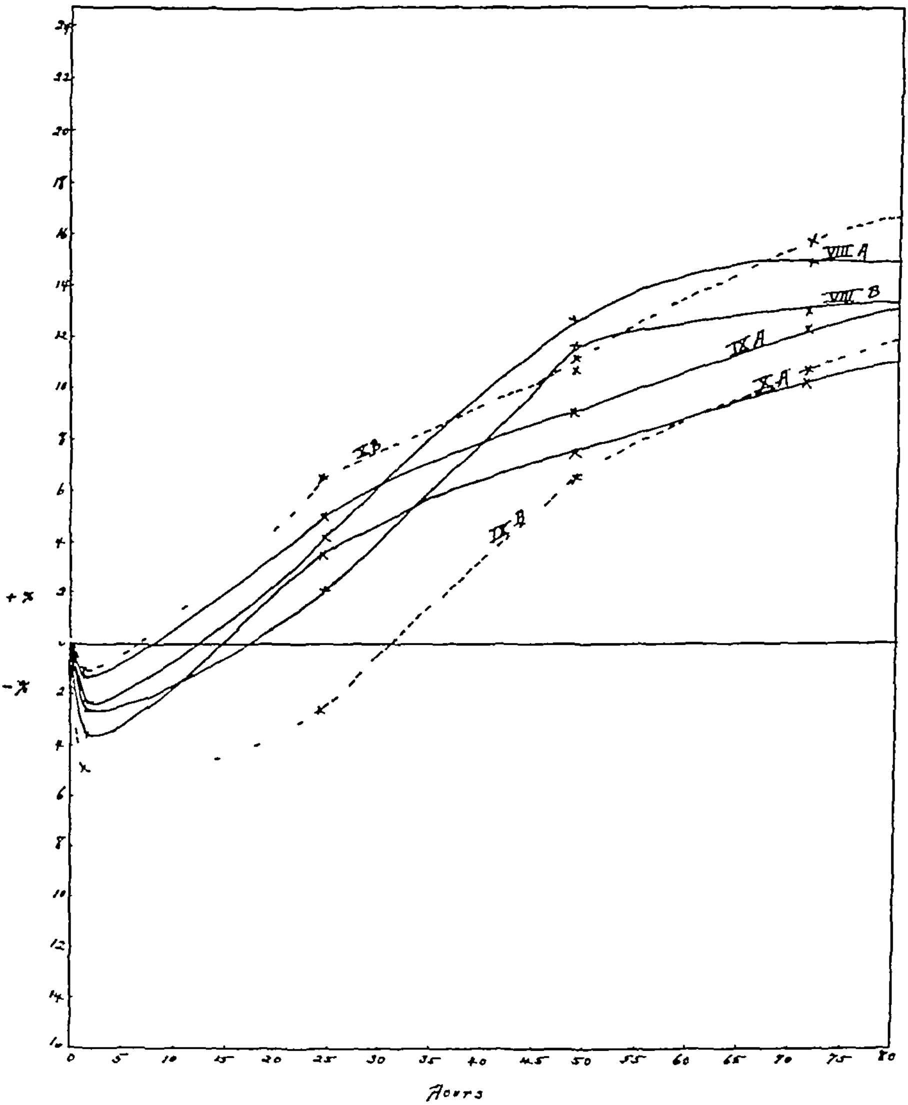

CHART III

———— Plasma from patient suffering from iodine poisoning No edema
- - - - - - Plasma from patient with cardic decompensation and edema ++++

muscles (VII A) Here again it is seen that the curves of the two muscles of each frog exhibit a tendency to approximate each other The greatest variation between two muscles of the same frog is noted for the muscles of frog V, which were in different kinds of plasma. But even in this case the dehydration curves of the two muscles and the imbibition curve from 45 to 75 hours are very similar

Chart III illustrates the curves of muscles placed in plasma from a patient with iodine poisoning and with no edema or history of cardiac or renal disease, and curves of muscles in plasma from a patient with extremely severe edema and cardiac decompensation The curves for muscles IX B and X B both in plasma from the edematous patient, illustrate the danger of concluding that the amount of imbibition depends solely upon the plasma, since at the twenty-fourth hour of immersion muscle X B shows the greatest, and muscle IX B the least gain in weight of any muscle in the experiment represented on chart III At the forty-eighth hour the greatest increase in weight is of muscle VIII A in the plasma of the non-edematous patient While curves or the two muscles of frog VIII follow each other closely, those of the muscles of the other two frogs show greater differences

In chart IV is seen a comparison between the rate of imbibition of muscles in plasma from a patient with slight pitting edema, and from one with severe edema The greatest initial loss of weight is noted in the two muscles of frog XI which were in the plasma of the patient with the greater edema The curves of these however cross those of the muscles XII A and XII B, which were immersed in plasma from the patient with the lesser edema, in from 45 to 65 hours

The futility of attaching any great significance to results which might indicate that the rate of imbibition is dependent solely upon the presence of edema in the individual from whom the plasma was taken, may be seen by a comparison of chart V with charts I and II, for chart V represents almost opposite results from those in charts I and II Three of the muscles (XIII A, XIII B, and XIV A) in the plasma from patient with no edema show greater imbibition than either of the muscles immersed in the plasma of the patent with the severe edema As further evidence of inconsistency of results as interpretable on a basis of differences in plasma, the curve of muscle XV A is not only considerably lower than that of any other muscles in the same plasma,

but at the twenty-fourth hour of immersion it is lower than any other curve regardless of plasma Later the curve crosses that of the other muscle of the same frog which was in the plasma of the non-edematous

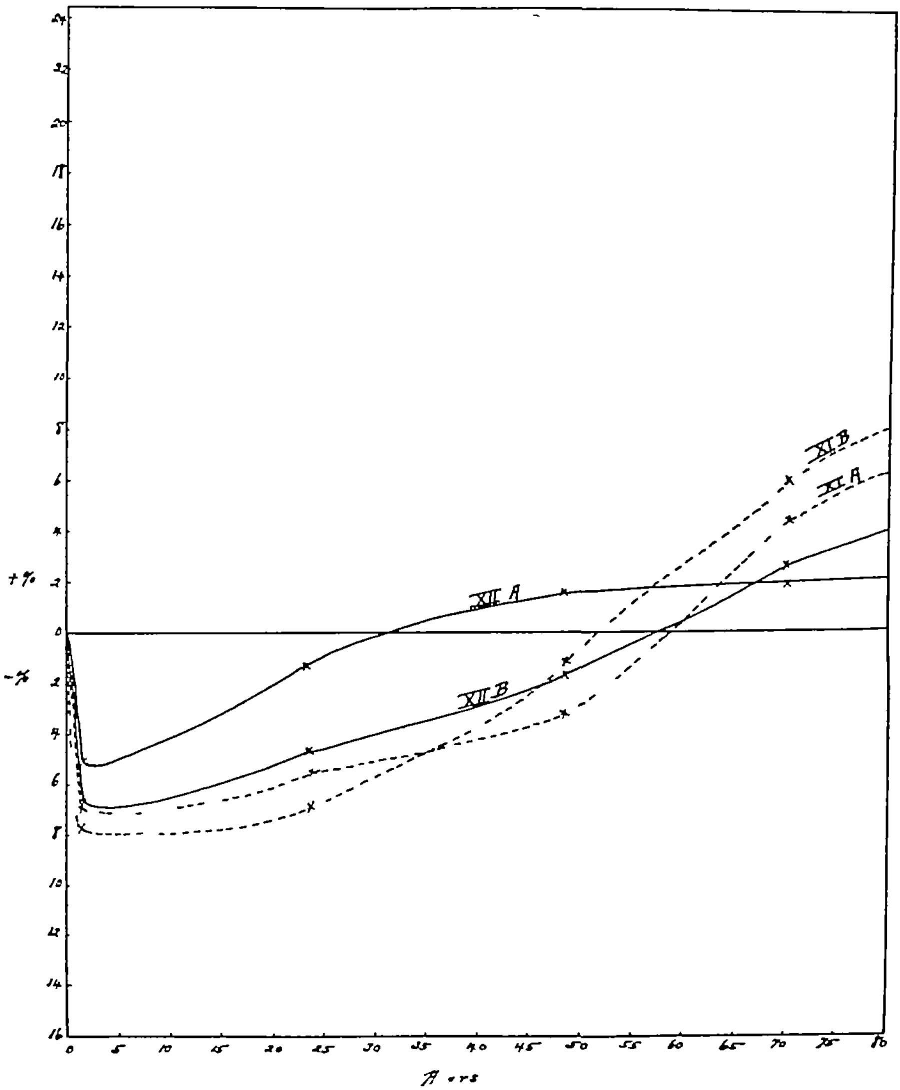

CHART IV

———— Cardiac decompensation with edema +++
———— Cardiac decompensation with edema +

patient Here again the curves of the two muscles of each frog tend to approximate each other, regardless of the plasma into which they were immersed

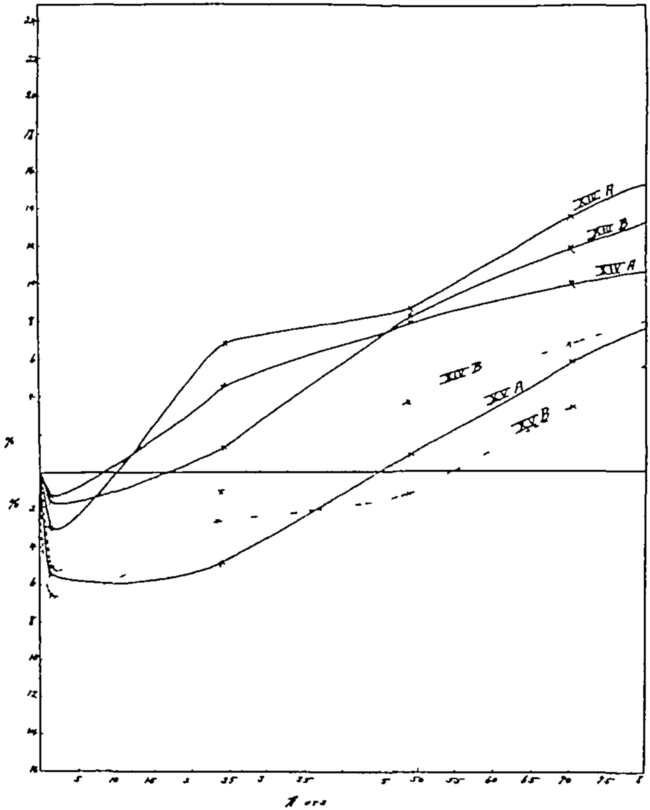

CHART V

———— Iodine and CO poisoning case No edema

- - - - - Plasma of patient with severe nephritis and edema ++++

Martin Fischer (4), in his book on Edema and Nephritis, suggests that the imbibition of fluid by tissues, as seen in the certain edemas, may be due to lack of oxidation in the tissues Since carbon-monoxide

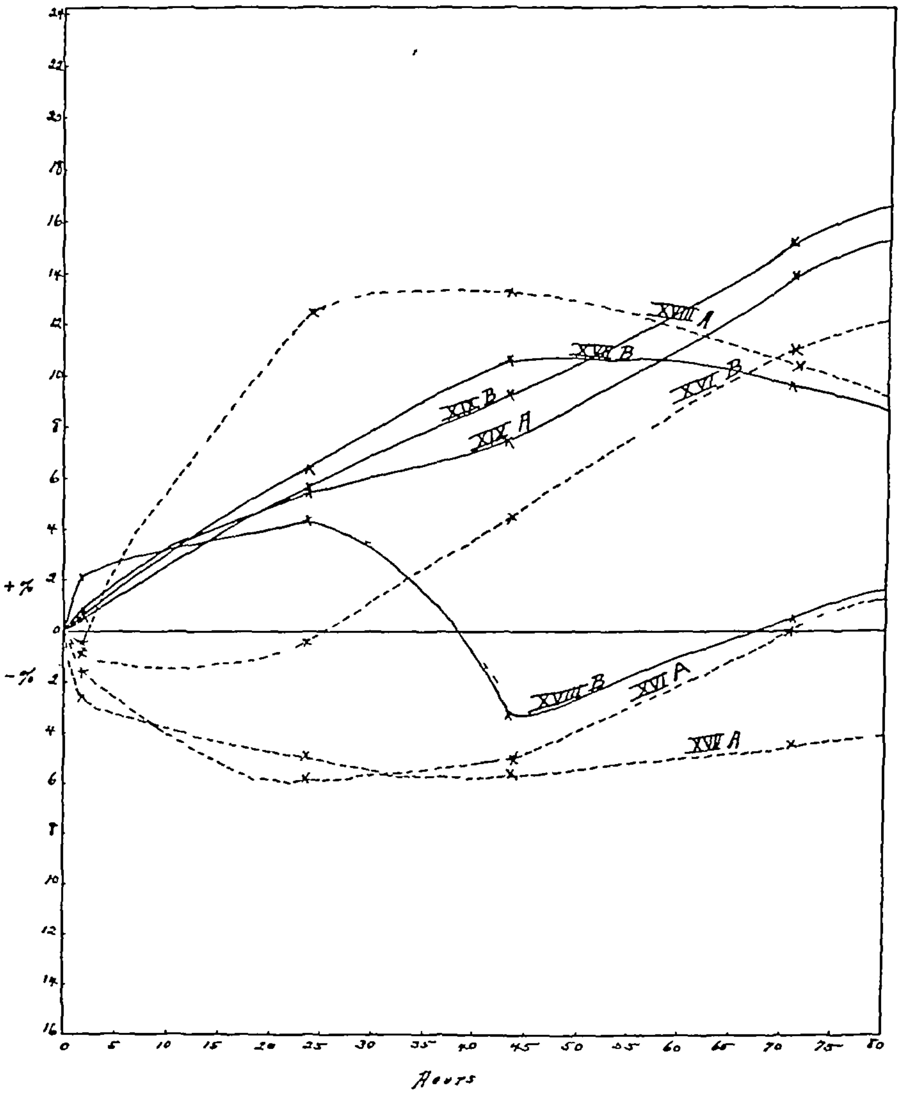

CHART VI

--------- 0 9 per cent sodium chloride solution

———— Mammalian Ringer's solution

poisoning is a condition in which the oxygen supply to the tissues is reduced, one might be led to believe that imbibition by the muscles in the plasma of the patient with carbon-monoxide poisoning (chart V) may have been influenced by this condition. On the other hand it is to be remembered that even in severe cases of carbon-monoxide poisoning, edema is never a directly associated finding. Also it may be noted, by comparison with the previous Charts, that the curves of the muscles in this plasma are no higher than many of the curves of muscles in plasma of other controls. The striking point in this chart and in some of the others discussed, is the low rate of imbibition by muscles in the plasma of a patient with marked edema.

Chart VI represents the imbibition curves of muscles placed in 0.9 per cent sodium chloride solution and in mammalian Ringer's solution. This chart illustrates very well the danger of attributing great significance to any results such as those reported by Labbé and Violle, or as previously seen in charts I to V. All of the muscles placed in 0.9 per cent salt solution lost weight during the first hour, while all of those placed in the mammalian Ringer solution imbibed fluid from the time of immersion. The rate of imbibition of muscle XVIII A in the sodium chloride solution is greatest, while the secondary dehydration of muscle B of the same frog, which was immersed in mammalian Ringer solution, we cannot explain. The crossing of the imbibition curves of muscles in the same and in different solutions causes one to hesitate to attribute any specific significance to the results previously discussed. The marked difference between the amounts of imbibition of the two muscles of frog XVI, in the identical solution, would indicate that slight differences in imbibition of muscles in different kinds of plasma may not safely be attributed to differences in the plasma.

That the rate of imbibition by the muscles depends to a large extent upon the state of isotonicity of the solution into which it is immersed, is indicated in charts VII and VIII. The curves for the muscles XXI B and XXII B in 0.45 per cent sodium chloride solution, which is hypotonic to frog's blood or plasma, show no dehydration but a marked imbibition beginning at once upon immersion. Three of the muscles in the frog Ringer's solution, which is nearly isotonic to frog fluids, lost weight during the first two hours, and did not regain their

34 per cent during the first hour, and from 64 to 73 per cent during the first 24 hours The curves for all of the muscles are strikingly

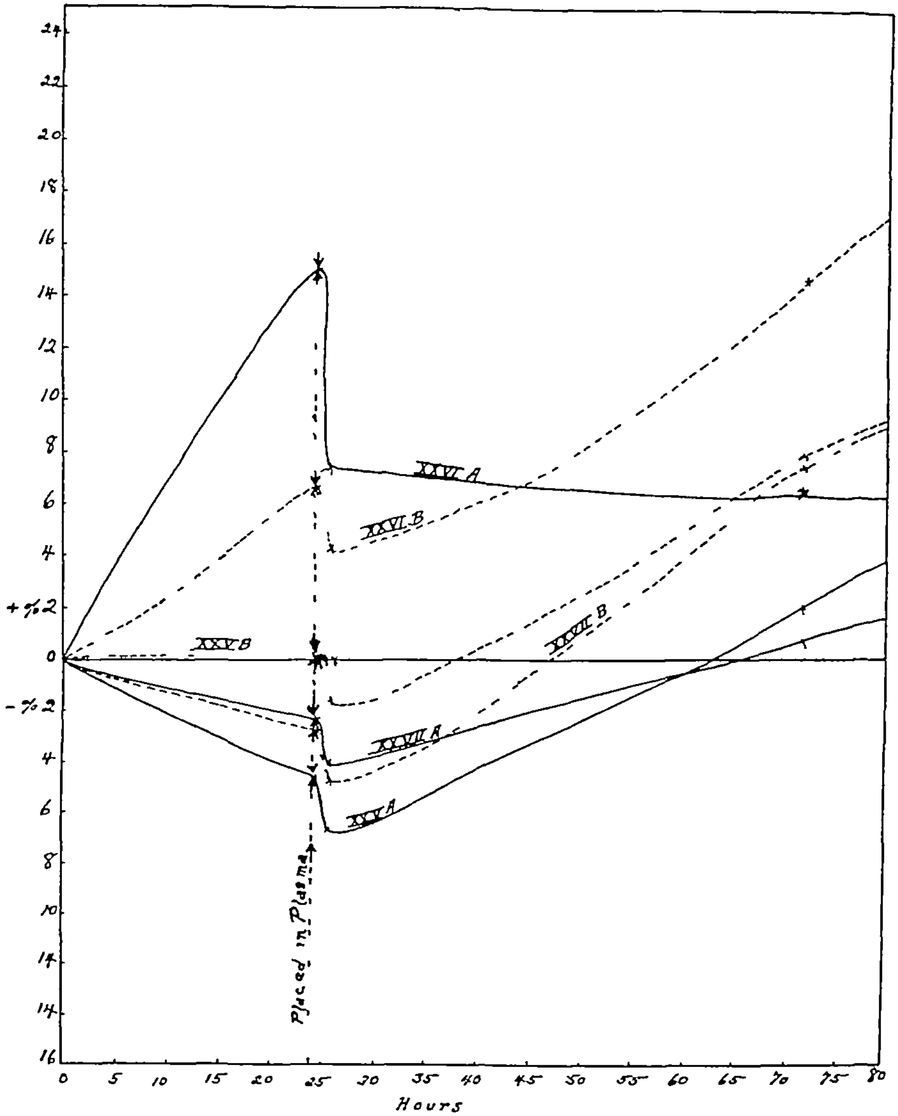

CHART IX

———— Plasma normal blood
———— Cardiac decompensation Edema +++
XXVI B ———— 0 9 per cent sodium chloride solution

similar, both in showing a rapid increase in weight of the muscles and a more gradual loss in weight after the first 24 hours

To test out the possibility suggested by the work of Martin Fischer (3), that imbibition by the muscles may be influenced by the production of acid products in them due to degeneration after removal from the frogs, we removed the gastrocnemii from a number of frogs and kept them in moist air in bottles for 24 hours before immersing them in the various fluids (see chart IX) The increase in weight of some of the muscles (XXVI A and XXVI B) while in the bottles may have been due to an excess of moisture in the bottles The immediate dehydration which occurred with immersing the muscles in the fluids is striking During the 24 hours, degenerative changes must have taken place, but instead of immediately imbibing fluid from the plasmas or salt solution all muscles lost weight when first immersed As all of the fluids of immersion were hypertonic to frog plasma, and as we have seen in previous charts that muscles placed in hypotonic solutions immediately imbibe fluid, a phenomenon which may be explained on a basis of osmosis, without initial dehydration, we are inclined to consider the initial loss in weight seen in chart IX as largely a matter of osmosis, but the subsequent imbibition is not so easily explained

Labbé and Violle reported that frog muscles placed in the fluid of pleural effusion without regard to the etiology of the condition also showed an increased power to take up fluid We were entirely unable to corroborate this finding In experiments in which we placed frog muscles in fluid of pleural effusions, the initial loss in weight was very similar to that seen when the muscles were placed in the blood plasma of the various types of patients, but the subsequent imbibition was very gradual, and at the end of 72 hours the muscles had increased in weight only from 0 3 to 2 5 per cent above their original weight Although we tried this in a number of cases, our results were always similar to those illustrated in chart X

Chart XI represents the imbibition curves of frog muscles placed in fluid taken from the abdominal cavity of a patient with portal cirrhosis of the liver The curves are seen to be very similar to those in the pleural effusion fluid

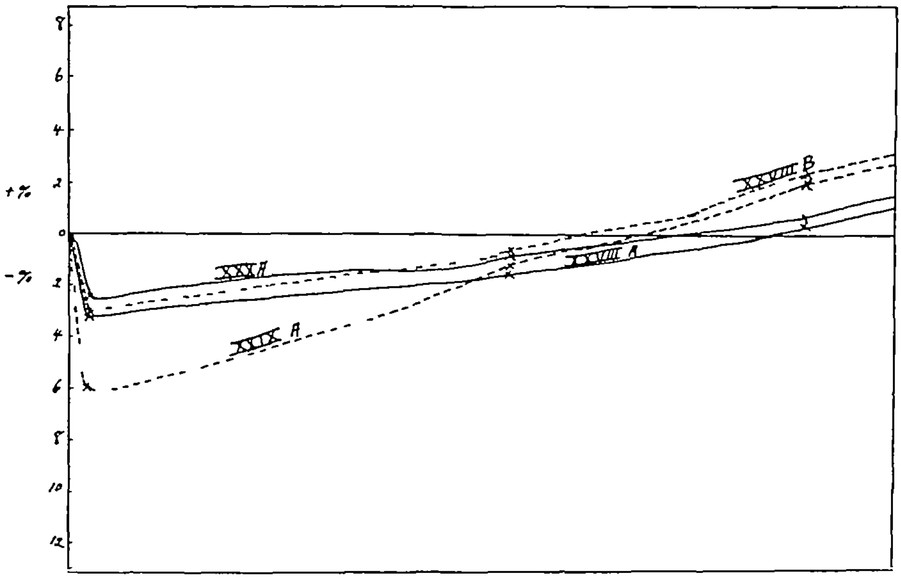

CHART X FLUID FROM PLEURAL CAVITY (PNEUMONIA)

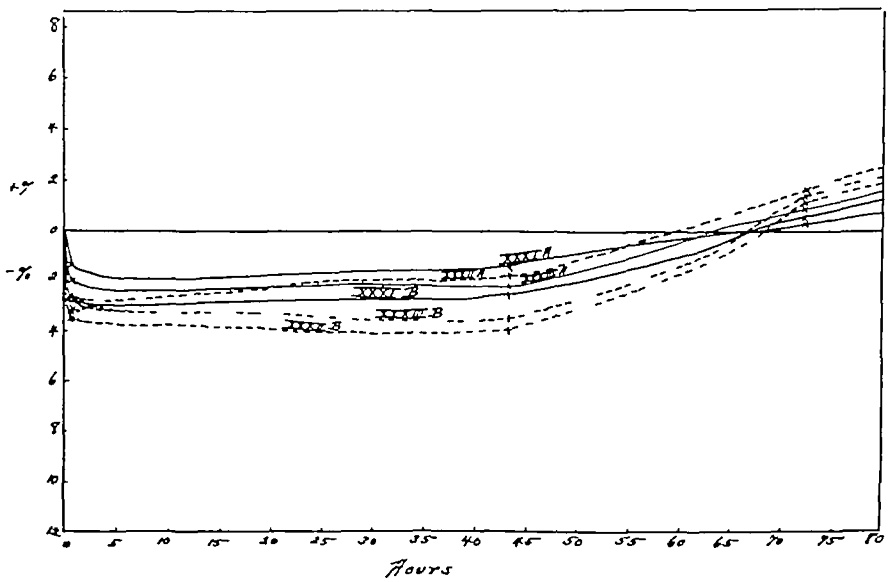

CHART XI FLUID FROM ABDOMINAL CAVITY (PORTAL CIRRHOSIS)

SUMMARY

Experiments, in which the rate of imbibition by frog muscles immersed in the plasma of edematous and non-edematous patients and in various other fluids was studied, were carried out with the following results

1 An initial loss of weight occurred in all frog muscles placed in blood plasma at 10°C regardless of whether that plasma was taken from a subject with edema or with no edema. This initial dehydration was, in some instances, greater in muscles placed in plasma from an edematous subject than in those placed in plasma of a subject without edema.

2 Although in some instances muscles placed in plasma of edematous subjects increased in weight more rapidly than did muscles in normal plasma, this was not a constant finding, since at times a muscle in normal plasma increased in weight more rapidly than did a second muscle of the same frog or a muscle of a different frog in the plasma of a patient who had a very marked edema

3 The imbibition curves of the muscles in the various specimens of plasma were too variable to permit of drawing any conclusions as to the influence of any particular type of plasma upon imbibition

4 In hypotonic salt solution frogs muscles showed marked imbibition without initial dehydration, while in hypertonic solutions there was an initial dehydration with subsequent slight or moderate imbibition

5 There was a tendency in most instances for the two muscles of the same frog to imbibe fluid at approximately the same rate, without regard to the fluid of immersion This was not a constant finding, for in several instances there was a considerable difference in the rates of imbibition of two muscles of the same frog in plasma from the same individual, whether that individual had edema or not

6 Frog muscles immersed in the fluid of pleural effusion, such as resulted from pneumonia, or fluid from the abdominal cavity of a patient with cirrhosis of the liver with portal obstruction, lost from 1 to 6 per cent of their weight during the first 1 or 2 hours, and very slowly regained their original weight in from 45 to 65 hours

7 The results of these experiments do not support the theory that

edema depends upon changes in the blood of such a nature that they increase the imbibition of fluid by the tissues bathed by this blood

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OXYGEN CONSUMPTION, OXYGEN DEBT AND LACTIC ACID IN CIRCULATORY FAILURE[1]

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The following investigation was undertaken in an attempt to ascertain some of the chemical changes in the functioning tissues which might develop from circulatory failure especially those which concern oxygen and lactic acid The disturbances of cellular metabolism which occur in circulatory failure have occupied a considerable amount of attention in recent years This subject has been chiefly studied in regard to the changes in the carbon dioxide content and combining power of the blood or to the changes in oxygen content of the arterial or venous blood These observations have contributed to our knowledge of some of the results and compensations which are consequent upon failing circulation but have not explained many of the phenomena which occur in this condition Since the principle symptoms in early disturbances of the circulation are produced by muscular effort, it seems reasonable to associate certain of them with related functions in the muscles themselves, more especially because investigations performed heretofore did not explain the cause of these symptoms The investigations of Hill and Meyerhof and their co workers into the physiology of muscular work indicated that similar observations in persons with disturbed circulation might help to elucidate this problem We have therefore repeated phases of their work in cases with disturbed circulation and have compared them with normal individuals under similar circumstances

Circulatory failure may be defined as a state in which the volume of blood circulated per unit of time is not adequate for the physical needs of the moment These needs may vary over a considerable

[1] Read before the Annual Meeting of the Association of American Physicians, at Atlantic City May 4, 1926

range of activities from that of complete rest up to considerable physical and mental activity The point at which physical effort becomes embarrassed differs in different individuals The question of a normal point or degree is impossible of an answer The work accomplished with ease by a youth of twenty could not be done by a man of sixty except with considerable effort and distress A conspicuous difference would, furthermore, be found in men of twenty in their capacity to do heavy physical work This would be dependent upon their "training," or in great part upon the functional efficiency of their circulation We consider that the normal capacity for physical effort should be taken to be the amount of work which can be accomplished by the average individual, taking into consideration his age, sex, and previous training It will be found that all so-called *healthy* individuals may be grouped between the trained athlete on the one extreme and the untrained sedentary worker on the other But there would be no reason to believe that the one could not be made into the other provided there were no pathological condition which would interfere If one were present, the individual could not be classified as *healthy*

When one comes to consider the capacity for physical exertion in conditions of circulatory disease, a still further graded result is obtained There are those cases which are little, if at all, different from the normal, but from this point cases may show all degrees of impaired circulatory function down to those where life is maintained with difficulty, and eventually death ensues from an inadequate volume of blood circulated Cases in all degrees of circulatory failure were investigated during the course of the work to be reported It was natural that only those with a comparatively moderate degree of circulatory deficiency were found to be capable of carrying out the exercise experiments The quantitative results obtained clearly indicated, however, the progressive character of the process Only cases with an uncomplicated rheumatic cardiac lesion were used for the exercise experiments, as it was considered essential that as far as possible cases in which there were lesions in other organs should be excluded in order not to complicate the observations Among the cases in which lactic acid determinations only were done the circulatory failure was due to a variety of lesions

METHODS

The principles of the methods employed in this work have already been elaborated in published experiments of a similar type on normal individuals (1), (2) and (3) The Douglas Bag method was employed throughout and deter minations of oxygen consumption, debt and requirement were made in exactly the same manner as was employed in these previous experiments

Two forms of exercise were used namely, walking and standing running It is well known that individuals with cardiac disease of any severity are unable to exert themselves to the same extent that normal persons can and the degree of these two exercises is consequently mild when judged by normal standards As will be seen later, as far as the patients themselves were concerned, even the "mild" exercises produced the same effects as are observed in and after severe exercise in healthy people Consequently the rate of walking was in most cases reduced to about 3½ miles per hour, and standing running was done at 184 steps per minute

Another precaution to which special attention had to be paid in these cases was that no exercise of *any* kind should be undertaken before the preliminary resting oxygen consumption was determined We were much puzzled at first by the differences in our initial and final resting oxygen consumption values, in spite of the fact that we had allowed what in normal individuals was an adequate preliminary resting period It eventually transpired that where these differences occurred the patients lived outside the hospital and had walked up the short hill from the street to the laboratory before the determination was made This apparently mild exercise was quite sufficient to cause these variations Follow ing this experience we chose as our subjects hospital patients who had been lying in bed twelve or more hours before the experiment was performed and who were brought in a wheel chair from their ward to the laboratory when required

The gas samples were analyzed in Henderson's modification of the Haldane apparatus, while the lactic acid in the blood was estimated by Clausen's method (4), using the modifications described by one of us (1)

OXYGEN INTAKE AND REQUIREMENT

As soon as an individual starts to take exercise of any kind the O_2 intake per minute rises The rise to the level required for the exercise is not instantaneous and is reached only after some two minutes have elapsed Each different degree of exercise requires, furthermore, a definite amount of O_2 intake which increases with the severity of the exercise, until a point is reached at which the heart and lungs are unable to meet the oxygen demand required for the

exercise In short, the O_2 demand or requirement[2] of the exercise is met until the O_2 intake is at a maximum Beyond this point the individual must go into O_2 debt[3] if the exercise is to be performed As a result of the accumulation of lactic acid during exercise extra oxygen is used during the recovery period to remove it This extra oxygen is of course the oxygen debt and the time taken to return to a normal O_2 intake is spoken of as the recovery period

In the patient with cardiac disease we would expect two variations to occur in the above scheme (*a*) In the first place, owing to the diminished output of the heart (5) (6) and (7) the amount of oxygen reaching the muscles per minute is diminished and therefore the O_2 intake will be at a maximum at a lower level than it is in the normal person (*b*) Secondly, again owing to this diminished output, the time required for the O_2 intake to reach the level for the exercise will be longer This will be most noticeable in exercises demanding a high level of O_2 intake

As regards this response to exercise, there is no essential difference between the cardiac patient and the normal individual it is one of degree only The cardiac patient is working on a lower level and this level will be lower and lower as the severity of the disease increases, until at length, as we shall see later, in entirely decompensated patients even at rest in bed the requirement may be more than the heart is able to cope with It is simply a question of the relationship between the O_2 intake and the amount of exercise that has to be done for, very probably, there is no difference between the processes required to run a mile in four minutes and to keep a normal tonicity in the muscles when at rest in bed Both require a certain amount of oxygen per minute and if this is not available the individual is bound to go into oxygen debt and show all the symptoms associated with this condition

[2] The oxygen requirement of a given effort is defined as the total oxygen used during the exercise and in complete recovery from it, reckoned from the resting level of oxygen consumption

[3] The oxygen debt is determined by measuring the *total* oxygen used in the recovery period, starting from the end of exercise and subtracting the oxygen which would have been used in the same period had the body remained at rest throughout

TABLE 1

A Walking experiments

Subject	Weight	Date	Exercise and duration	Excess O_2 intake	O_2 requirement	O_2 debt
	kilos			*cc. per minute*	*cc. per minute*	*cc.*
L. Normal male	70	March 16, 1926	Walking at 1 42 metres per second for 7 minutes 20 seconds	636	(750)	177
		March 17, 1926	Walking at 1 7 metres per second for 5 minutes 10 seconds	1,189	(1,000)	1,140
		March 19 1926	Walking at 2.02 metres per second for 4 minutes 16 seconds	1,408	(1,400)	909
R. Chronic mitral endocarditis with stenosis and insufficiency (rheumatic)	74	February 16, 1926	Walking at 1 42 metres per second for 7 minutes 24 seconds	735	(750)	627
		February 17, 1926	Walking at 1 7 metres per second for 5 minutes 18 seconds	1,142	(1,000)	1,828
		February 18, 1926	Walking at 1 7 metres per second for 3 minutes 12 seconds	1,142	(1 000)	2,271
		February 19, 1926	Walking at 2.02 metres per second for 4 minutes 16 seconds	1,380	(1,400)	3,415
Miss H. Normal female		November 27, 1925	Walking at 1 04 metres per second for 7 minutes	670	(600)	580
		December 3 1925	Walking at 1.25 metres per second for 7 minutes 30 seconds	476	(600)	620
		December 1, 1925	Walking at 1.36 metres per second for 7 minutes	566	(600)	1 194
Miss Ld. Chronic mitral endocarditis with stenosis and insufficiency (rheumatic)		December 31, 1925	Walking at 0 96 metres per second for 7 minutes	500	751	1 440
		December 31, 1925	Walking at 0 96 metres per second for 6 minutes	486	751	1,600
		December 29, 1925	Walking at 0 96 metres per second for 6 minutes	600	751	1,400

* The excess oxygen intake is the extra oxygen used per minute over and above the resting oxygen intake.

TABLE 1—*Continued*

B Standing-running at 184 steps per minute

Subject	Weight	Date	Exercise and duration	Excess O_2 in take*	O_2 require-ment	O_2 debt
	kilos			*cc per minute*	*cc per minute*	*cc*
L Normal male	70	March 5, 1926	Standing-running at 184 steps per minute for 3 minutes	2,549	3,286	3,540
		March 9, 1926	Standing-running at 184 steps per minute for 3 minutes	2,354	2,145	1,528
		March 12, 1926	Standing-running at 184 steps per minute for 3 minutes	2,061	2,295	2,210
R Chronic mitral endocarditis with stenosis and insufficiency (rheumatic)	74	February 22, 1926	Standing-running at 184 steps per minute for 3 minutes	1,851	4,073	8,270
		February 24, 1926	Standing-running at 184 steps per minute for 3 minutes	1,622	3,267	5,417
		February 26, 1926	Standing-running at 184 steps per minute for 3 minutes	1,716		
		March 2, 1926	Standing-running at 184 steps per minute for 3 minutes	1,876		

We have studied this relationship between O_2 intake and O_2 requirement in patients[4] with moderately severe cardiac lesions and compared the findings with those obtained on normal individuals Both males and females were used as subjects The results of our experiments are seen in table 1 Some of the data (in parentheses) are taken from earlier experiments on H L (3, p 168, fig 2) and represent figures for a normal individual of about 70 kilos weight These approximate estimations are indicated by being in parentheses

Let us consider first the results of the walking experiments on L and R At all the observed speeds L is obviously not distressed

[4] Observations were carried out on a large series of cases but only a few complete results are recorded here in detail. All of the experiments revealed the same general results but varied in degree in different cases

His oxygen intake is well below its maximum value, that is to say about 4 0 liters per minute (3, p 156, table 1) and the requirement (3, p 168, fig 2) of the exercise is met with ease so that the O_2 debt acquired is small and his recovery rapid R presents a very different picture In his case, although his O_2 intake for the different speeds is approximately the same as L's, yet his O_2 debt is much larger, and at the highest rates of walking is very large when it is considered that the maximum speed studied is only 2 02 meters per second, i e , about 4½ miles per hour If we assume, as we have, that the O_2 requirement of the exercises is the same in his case as in L's, then the only explanation for these large debts is that his circulation responds much more slowly to the demands of the exercise than it does in the normal individual This means that although he finally comes into equilibrium he takes so long to do it, compared with a normal man, that a considerable oxygen debt has time to accumulate This, as we shall see, does occur (cf fig 1) In the case of the females, H and Ld, an exactly similar result was obtained

In the standing running experiments in addition to this second factor, the first factor which was predicted seems to come into operation, that is to say, the lower limit of the maximum oxygen intake in cardiac disease. These experiments are possibly not as accurate as the walking ones since in the latter uniformity of exertion is more easily obtained Every endeavor was made, however, in the standing running experiments to secure this by warning and instructing the subjects to lift their knees to the same height at each step This was arbitrarily set at a point where the thigh was flexed to a right angle with the body The objective symptoms on exercise were in themselves significant L did exercise at the set rate, that is to say 184 steps per minute, with practically no discomfort, and soon recovered afterwards R, on the other hand, was always greatly distressed and usually had to be more or less driven to complete it. In addition his recovery was long and was initially marked by exhaustion and dyspnea These signs are reflected in the results for R L's oxygen intake averaged around 2 3 liters a minute and his oxygen debt around 2 4 liters (table 1 B), while the respective values for R were 1 8 and 6 8 liters respectively (table 1 B) In view of the large O_2 debt we can assume that about 1 8 liters a minute is R's maximum

oxygen intake and since the oxygen requirement is around 3 0 to 3 5 liters a minute this in itself would account for all or a large part of the observed debt, and when considered along with the increased debt due to the circulatory lag is about the expected value

TABLE 2

*Subject L Normal Aged 25 Weight 70 kilos Post-absorptive**

Exercise Standing-running 184 steps a minute for 3 minutes

Initial respiratory exchange $\frac{CO_2}{O_2} = \frac{240}{281} = 0\ 85$

Mid point of sample	Excess O_2 intake
seconds	*cc. per minute*
7 5	869
22 5	1,549
37 5	2,079
52 5	2,139
75	2,629
105	2,144 (?)
135	2,890
165	2,629

Subject R Chronic endocarditis with mitral stenosis and insufficiency (rheumatic) Aged 34 Weight 74 kilos Post-absorptive

Exercise Standing-running 184 steps a minute for 3 minutes

Initial respiratory exchange $\frac{CO_2}{O_2} = \frac{208}{266} = 0\ 78$

Mid point of sample	Excess O_2 intake
seconds	*cc per minute*
7 5	472
22 5	784
37 5	1,028
52 5	1,183
75	1,419
105	1,608
135	1,719
165	1,796

* The term *post-absorptive* implies that the subject had been without food for at least twelve hours before the experiment.

Hill, Long and Lupton in their papers (1), (2) and (3) class exercise at this speed as a moderate one which should have an oxygen

debt of 2 to 3 liters and a recovery period of 30 minutes As seen above, L fulfills this but R presents quite definitely the picture of an individual who has undertaken severe exercise comparable in the normal individual to standing running at a much higher speed than has been carried out in the experiments reported here, that is to say, 237 steps per minute for about the same time It is interesting to note that R was tried at this rate and found quite incapable of performing it for more than a few seconds

In order to test the second postulate that one of the causes for the

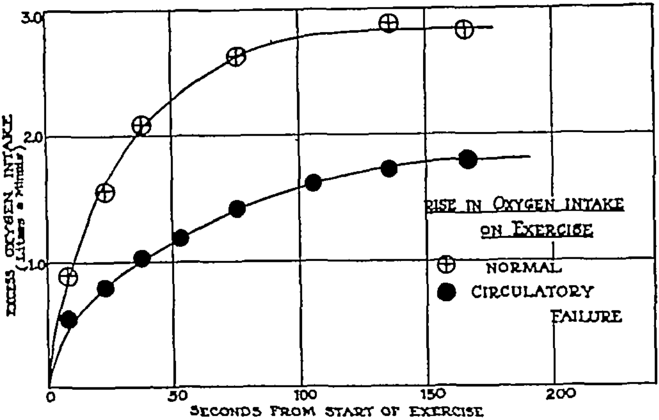

FIG 1 CHART OF DATA IN TABLE 2

increased oxygen debt in the cardiac cases was the circulatory lag in the response to exercise, we have determined the rise in oxygen intake on exercise in such cases and also in normal individuals The results are in table 2 and figure 1

These show quite clearly the greater initial lag in the cardiac patient's response to exercise The curve in these cases lacks the smart initial response that is seen in the normal and is altogether a much slower and gradual rise to a maximum Naturally, the greater level of O_2 intake reached by the normal rather exaggerates the dif-

ference between the curves, nevertheless, allowing for this, the difference in the shape of the curves is obvious

OXYGEN DEBT IN CIRCULATORY DISEASE

This has already been considered to some extent in the preceding section, and we have seen that for a *given exercise* this quantity is greater in individuals with circulatory disease than it is in normal persons, owing to the slower circulation rate in the former If the *maximum* oxygen debts are considered, we find that the above order of magnitude is reversed The maximum O_2 debt of an individual represents the greatest extent to which he can drive his musculature

TABLE 3

Maximum oxygen debts

(a) Normal individuals			(b) Cardiac cases		
Subject	Exercise	O_2 debt	Subject	Exercise	O_2 debt
		liters			*liters*
A V H	Running fast for 8 minutes	10 9	R	Standing-running 184 steps per minute "all out" for 3½ minutes	5 4
C N H L	Stool jumping for 2 minutes	10 5	B	Standing-running 184 steps per minute "all out" for 3½ minutes	6 0
D T	Running ¼ mile very fast	13 2	R	Standing-running 184 steps per minute "all out" for 3½ minutes	8 4
T A L	Standing-running "all out" for 3½ minutes	10 1			

before total exhaustion occurs In other words it is the greatest accumulation of lactic acid the body will tolerate This definition would imply that this quantity was independent of the circulation and, theoretically, it is In addition, by actual experiment, it has been shown that when exhaustion is reached the muscles contain about as much lactic acid as does an isolated muscle when stimulated until it will no longer respond Theoretically then, we should expect to find that by long continued exercise the cardiac patient would develop a maximum oxygen debt equal to that of a normal individual, the only difference being the rate at which it was accumulated owing, of course, to the slower circulation rate Practically, our cardiac

cases have never shown values for a maximum O_2 debt anywhere approaching those that have been recorded for normal individuals Table 3 shows maximum values in the two cases

TABLE 4

Subject L. Normal Aged 25 Weight 70 kilos

Exercise Standing running at 184 steps a minute for 3 minutes

Resting respiratory exchange $\frac{CO_2}{O_2} = \frac{248}{277} = 0.89$

Mid point of interval	Excess O_2 intake
	cc per minute
0	2,321
15″	1,690
1′	737
2′ 30″	77
5′ 30″	54
8′	45
15′ 30″	Nil
26′ 30″	13

Subject R. Chronic mitral endocarditis with stenosis and insufficiency (rheumatic) Aged 34 Weight 74 kilos

Exercise Standing running at 184 steps a minute for 3 minutes

Resting respiratory exchange $\frac{CO_2}{O_2} = \frac{265}{300} = 0.87$

Mid point of interval	Excess O_2 intake
	cc per minute
0	1,622
16″	1,330
1′	1,033
2′ 30″	351
5′ 30″	321
8′	141
15′ 30″	63
35′ 30″	34
55′ 30″	2

Quite probably the reason for these differences is a psychological one. The cardiac patient is aware of his infirmity and dreads to drive himself too far for fear of the consequences

THE RECOVERY PROCESS IN CIRCULATORY DISEASE

The foregoing considerations enable us to predict the difference in the recovery process to be found here between normal and diseased individuals The larger oxygen debts imply a longer recovery period as also does the slower circulation rate These theoretical considerations are well substantiated by our results, as table 4 and figure 2 show

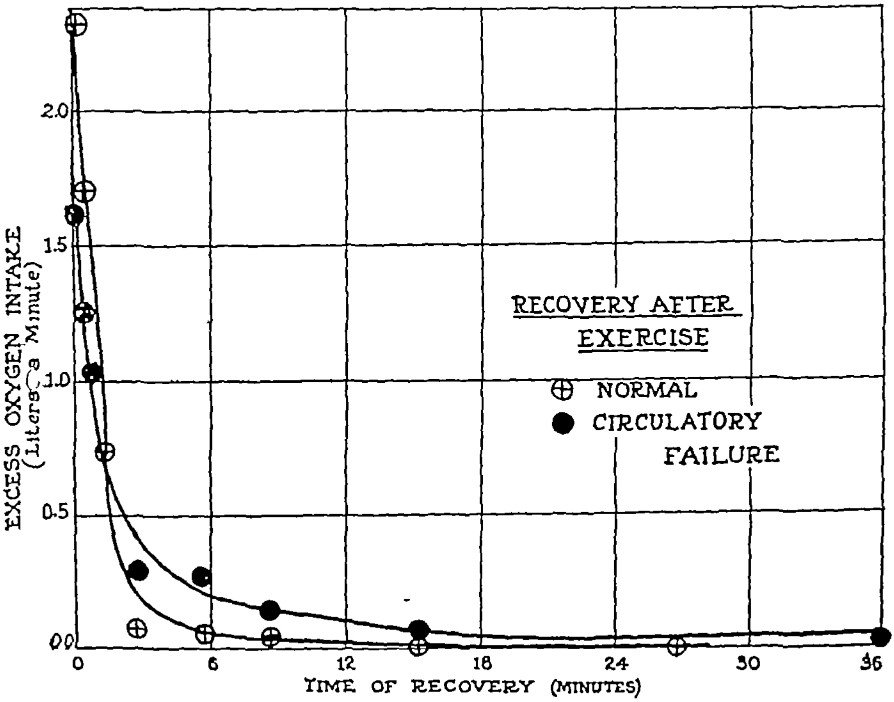

FIG 2 CHART OF DATA IN TABLE 4

The recovery period in L is strikingly shorter and more rapid than in R in spite of its higher initial level It is easy to see that with the increasing circulatory failure recovery from even mild exercise becomes slower and more prolonged until, as we shall see in completely decompensated cases, this is so lasting as to constitute an almost "chronic" condition of oxygen debt

LACTIC ACID IN THE BLOOD IN CIRCULATORY DISEASE

Although this subject is considered after the respiratory phenomena, its logical position should perhaps be first, for it is the appearance and disappearance of this substance in the body during exercise that is responsible for most, if not for all, of the phenomena

TABLE 5

Lactic acid in the blood after exercise in normal individuals and in patients with cardiac disease

Number	Condition	Exercise	Time of observation	Lactic acid in blood
				mgm. per 100 cc
1	Normal	Standing running 156 steps per minute for 55 minutes	Rest	20
			After 18 minutes exercise	58 1
			After 37 minutes exercise	52 5
2	Normal	Running at 9 miles per hour	Rest	23 2
			1 minute after exercise	54 6
3	Normal	Standing running 237 steps per minute for 10 minutes	Rest	21 0
			1 minute after exercise	95 0
			48 minutes after exercise	41 0
4	Normal	Walking at 4 1 miles per hour for 33 minutes	Rest	21 4
			1 minute after exercise	58 9
5	Cardiac disease	Walking at 3.81 miles per hour for 3 minutes 12 seconds	Rest	25 2
			1 minute after exercise	59 1
6	Cardiac disease	Standing running at 189 steps per minute for 3 minutes 1 second	Rest	40 6
			1 minute after exercise	167 2
7	Cardiac disease	Standing running at 189 steps per minute for 3 minutes	Rest	43 6
			1 minute after exercise	93 0
8	Cardiac disease	Walking at 3 4 miles per hour for 7 minutes	Rest	25 3
			1 minute after exercise	61 8

connected with that act The capacity for its accumulation in the muscles, and hence in the blood, enables the individual to perform exercise far beyond his contemporary oxygen supply its removal is the essential feature of the recovery process. Whilst it is not possible to study the changes of this substance in the muscles themselves, alterations of its concentration in the blood can give us considerable

information as to an individual's response to exercise As a general rule, a rise of lactic acid in the blood to more than 60 mgm per 100 cc on exercise signifies that this exercise is causing an increasing oxygen debt, or, in others words, that it is beyond the power of the individual to perform for any appreciable length of time

It was quite easy in our patients to take blood samples immediately at the end of exercise and to see how the lactic acid content compared with that of normal individuals under the same conditions The results are given in table 5

It is apparent from this table that for a given exercise the cardiac patient has a higher level of lactic acid in his blood than has the normal person The normal values are taken from the paper by Hill, Long and Lupton (1) This higher level necessarily implies a longer time to return to the resting value, and while this has not been actually measured our observations on the recovery time for oxygen tell us that this is actually so

OXYGEN CONSUMPTION AT REST IN CASES WITH SEVERE CIRCULATORY FAILURE

It has been pointed out above that the recovery period from exercise may be greatly prolonged If recovery were not complete after a night's rest in bed then it would be expected that a cumulative condition of oxygen debt would be produced This could only be removed by continuous rest in bed and days might be required to complete the recovery period A further and aggravated state would be that which might occur when even on prolonged rest an oxygen debt continued to develop It might be considered possible to detect this decrease in oxygen consumption as compared to the oxygen requirement by repeated determinations of the oxygen consumption under basal conditions But we are confronted in these abnormal states with the difficulty of determining the basal oxygen requirement The rapid and fictitious physiological changes in weight make a theoretical standard according to surface area almost an impossibility It therefore remains to carry out a series of almost daily estimations of the oxygen consumption irrespective of the theoretical surface area as an experiment unto itself But this has been fraught with difficulties which are inherent in the condition It has been

adequately demonstrated by Peabody, Meyer and Dubois (8) that patients with advanced circulatory failure have an increased oxygen consumption under basal conditions which they attribute to the increased physical effort resulting from dyspnoea which occurs even when at complete rest. This has been confirmed by other workers Under these circumstances it would appear to be difficult to determine a comparative oxygen requirement during the various stages of circulatory failure, as a comparative study is so far possible only in regard to the oxygen consumption If we take as proven, therefore, that with the increased respiratory effort consequent upon a failing circulation the oxygen consumption should be increased to meet the increased oxygen requirement, we would expect a progressive increase in the basal oxygen consumption If there is no increase, we arrive at the logical conclusion that the oxygen consumption is falling behind the oxygen requirement and results, consequently, in a progressive oxygen debt A number of attempts were made in properly selected progressive cases to learn whether these are the facts A typical example is shown in table 6

TABLE 6

Basal oxygen consumption in a case of chronic mitral endocarditis with stenosis and insufficiency with circulatory failure

Date	Oxygen consumption	Condition
	liters per hour	
February 13 1926	14 12	Moderate decompensation
February 17 1926	13 68	Improving
February 18, 1926	11 69	Improving
February 25 1926	12 68	Stationary
March 5, 1926	13 25	Stationary
March 17 1926	12 41	Much weaker, steady decline

During a period of apparent improvement of the circulation, the basal oxygen consumption declined to 11 69 liters per hour But subsequently there was a slight but consistent increase in the basal oxygen consumption to 13 25 liters Symptoms of circulatory distress then increased and, eventually, reached a climax and serious signs of circulatory failure developed Synchronously the oxygen consumption declined to 12 41 but other signs of oxygen debt developed

We are dealing here apparently with a condition where the margin of safety is very narrow and the comparatively gross methods of determination of oxygen consumption as compared with oxygen requirement are not sufficiently delicate to warrant definite conclusions The premises upon which we would base our conclusions in regard to these findings are, furthermore, not sufficiently consistent in their interpretation to be of value These results may be used to support an argument in two opposite directions as follows (1) If the oxygen consumption increases, it might indicate greater deficiency in the circulation with its resultant dyspnea and accompanying increase of physical exertion (2) On the other hand, a decrease in the oxygen consumption might indicate either a decreased need for oxygen due to improved circulation or else a complete breakdown of the circulation It is impossible to determine therefore whether decrease in the oxygen consumption indicates a decrease in the power of the circulation to provide the tissues with a sufficient amount of oxygen to meet the average requirement, or decrease in the requirement owing to improvement in the circulation relieving the dyspnea

LACTIC ACID IN THE BLOOD IN CIRCULATORY FAILURE AT REST

It seemed advisable therefore to seek some other index of failing circulation independent of such paradoxical interpretations as those resting upon the oxygen consumption To obtain such we have resorted to an index of oxygen consumption in the muscle mass It has been demonstrated by Meyerhoff (9) and Hill (10) that the oxidation of lactic acid resulting from muscular activity is dependent upon the oxygen supply to the tissues If this be deficient and an oxygen debt occurs then there is an increase in the lactic acid in the muscles, which is eventually reflected by an increase in the lactic content of the blood

As we have pointed out above, the state of persons with circulatory failure would seem to be equivalent to a continuation, with an accumulative effect, of the ordinary recovery processes from exercise This could be determined either through demonstrating that the oxygen consumption is greater than the oxygen requirement or that there is a lactic acid accumulation in the blood The former we found impossible of demonstration on account of the absence of a

TABLE 7

Lactic acid in the blood

Number	Sex	Age	Diagnosis	Date	Lactic acid in blood	Condition	Result
					mgm. per 100 cc.		
1	M	40	Rheumatic carditis	January 21 1926	56 0	In extremis	Died January 23, 1926
2	M	32	Rheumatic carditis and auricular fibrillation	January 11, 1926	48 1	Very serious	
				January 15, 1926	28 3	Improved	Died suddenly January 17, 1926
3	F	48	Aortic and mitral endocarditis	February 17 1926	46 1	Very serious	Died February 22 1926
4	F	49	Cardiac renal disease	January 27, 1926	41 7	Very poor	Discharged slightly improved
5	M	75	Arteriosclerosis, bundle branch lesion	February 17, 1926	40 0	Serious	Died March 8 1926
6	M		Syphilitic aortic disease	February 24, 1926	39 0	Very serious	Discharged to incurable home
7	F	23	Mitral stenosis	February 17, 1926	36 7	Very poor	Discharged slightly improved
8	M	22	Chronic mitral endocarditis with stenosis and insufficiency, and auricular fibrillation	April 1, 1916	34 6	Serious	Discharged home against advice
9	M		Chronic mitral endocarditis with stenosis and insufficiency and auricular fibrillation	January 7, 1926	28 4	Fair	
				January 27 1926	25 8	Unchanged	
				February 24, 1926	27 0	Unchanged	
				March 25 1926	22 9	Improved	Died suddenly May 10, 1926 of cerebral embolus
10	M	58	Chronic cardiac failure	January 27, 1926	26 6	Paroxysmal dyspnoea	Discharged home
11	M	22	Aortic and mitral endocarditis and delayed conduction time	February 22, 1926	25 0	Dementia precox	Taken home against advice
12	F	42	Mitral endocarditis and auricular fibrillation	January 27, 1926	24 0	Walking about	Discharged home
13	F	53	Aortic and mitral endocarditis and auricular fibrillation	January 27, 1926	21 6	Fair condition	Discharged improved
14	F	29	Aortic and mitral endocarditis	January 27, 1926	16 4	Walking about	Discharged home

base line The latter we could determine with accuracy In table 7 is tabulated the lactic acid content of the blood in cases of circulatory failure of different degrees of severity

It will be noted that the more severe the symptoms of failing circulation the higher the lactic acid percentage With improvement in the condition of the circulation the lactic acid content of the blood appeared to return to normal level This is well illustrated in table 8

This patient had severe circulatory failure, due to a rheumatic

TABLE 8

Lactic acid in the blood in a case of progressive circulatory failure with exacerbations and remissions in a case of chronic rheumatic mitral endocarditis with stenosis and insufficiency

Date	Lactic acid in blood	Condition
	mgm per 100 cc	
January 7, 1926	35 8	Symptoms of decompensation moderate
January 11, 1926	51 8	Symptoms more severe
January 15, 1926	29 8	General condition much improved
January 27, 1926	30 5	Pronounced dyspnea and orthopnea
January 28, 1926	110 0	Condition much worse almost moribund
January 29, 1926	38 7	Great improvement in condition
February 17, 1926	35 3	Condition has remained unchanged
February 24, 1926	30 3	Condition unchanged
March 13, 1926	27 7	Condition weaker more dyspnea and edema
March 18, 1926	105 1	Condition gradually became worse, now in extremis
March 25, 1926	49 8	Condition somewhat improved but very weak
March 26, 1926	40 3	Condition unchanged
March 27, 1926	108 5	Condition very bad, unconscious, died 12 hours later

carditis with mitral stenosis and insufficiency There was a succession of exacerbations of the circulatory symptoms with tricuspid insufficiency, increase of the dependent anasarca and jaundice With each increase of the circulatory failure there was a pronounced increase of the lactic acid in the blood This is well demonstrated in figure 3

The increase in severity of the symptoms on each occasion was more gradual than the rapid change in the concentration of lactic acid would indicate, while the remissions were equally gradual and

always followed treatment directed to relieve some cause of circulatory embarrassment, such as paracentesis of the peritoneum or pleura, phlebotomy or an increase in the amount of digitalis administered. The almost explosive character of the lactic acid fluctuations seems to indicate that points were reached in the degree of circulatory failure where the margin of safety had practically disappeared For analogy they may be compared to the course of events in a healthy man during running In such a person the lactic acid content of the

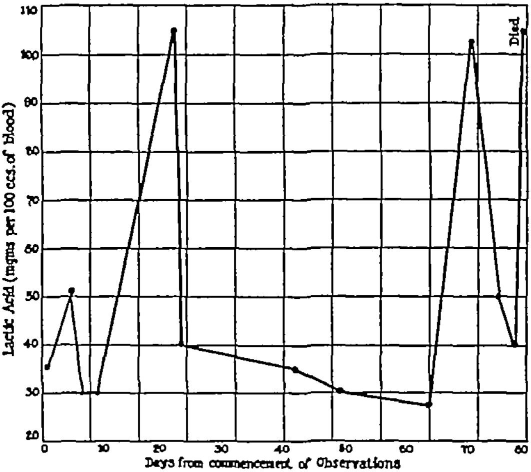

FIG 3 LACTIC ACID IN THE BLOOD IN THE CASE OF CHRONIC RHEUMATIC ENDOCARDITIS THE DATA ON WHOM ARE GIVEN IN TABLE 8

blood may remain constant, but at a higher level than normal provided he be in a steady state If now the exercise be increased so that the steady state is not maintained then a rapid lactic acid accumulation occurs The situation would appear to be similar in patients with severe circulatory failure A steady state is maintained at rest, but with a higher level of lactic acid than the resting healthy person If instead of increasing the exercise the circulation be reduced, then the steady state is no longer maintained and a rapid lactic acid accumulation occurs It is shown in figure 3 how the

recovery period after each exacerbation of circulatory failure becomes longer and less complete than after the previous one

It is suggested that the ultimate cause in circulatory failure may be due to lactic acid accumulation in the myocardium The experiments of Katz, Kerridge and Long (11) demonstrate that the muscle of the heart is less capable of acting as a buffer than is the skeletal muscle Lactic acid accumulation leads to decreased power of concentration which in the case of the myocardium produces a decreased blood supply which in turn leads to further lactic acid accumulation Thus a vicious circle ensues which tends to perpetuate itself but which promptly ceases once it has been cut by allowing the circulation to improve in spite of the increase of lactic acid The manner in which this may be brought about varies in different cases

THE INFLUENCE OF LACTIC ACID ACCUMULATION IN DYSPNEA

From time to time there has been controversy as to whether in circulatory failure the dyspnea so commonly found is due to an increase of the H-ion concentration of the blood Lewis, Ryffel, Cotton and Barcroft (12) came to the conclusion through observing a shift in oxyhemoglobin curves to the right that an increase in H-ion concentration did occur They were unable however to demonstrate the presence of lactic, β-oxy-butyric or other acid in the blood This was probably due to the technical difficulties encountered at that time But even the pronounced increase of lactic acid found in the cases here reported would not be sufficient except in the most severe instances to produce a conspicuous shift in either the carbon dioxide or oxy-hemoglobin dissociation curves It must be appreciated, however, that the concentration of lactic acid in the blood is but a reflection of the accumulation of lactic acid in the tissues from which it has escaped The processes which are occurring in the tissues produce the signs and symptoms of circulatory failure and these develop in large part from a defective blood supply

CONCLUSIONS

1 The response of an individual with circulatory failure is the same as that of a normal individual except in the following details

a There is a lag in the rise of oxygen intake to the level required for the exercise

b The maximum oxygen intake is set at a lower level than in a normal person for the same exercise

c The recovery period from exercise is more prolonged

d The rise in the lactic acid level of the blood is greater on a given exercise than in normal individuals

2 It was found impracticable to use basal oxygen consumption to determine a relation between oxygen intake and oxygen requirement.

3 Severe circulatory failure is accompanied by an increased rise in the level of the resting lactic acid in the blood

4 This accumulation of lactic acid in the blood is in proportion to the severity of the circulatory failure

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THE CONCENTRATION OF UREA IN THE BLOOD OF NORMAL INDIVIDUALS[1]

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The concentration of urea may be determined more easily and with greater accuracy than that of any other non protein nitrogenous constituent of the blood We have shown elsewhere (1) that the blood urea concentration ordinarily increases little above its usual level until the amount of functioning renal tissue has been reduced by more than half Since a decreased renal function is not of immediate importance to the patient until such a degree (50 per cent) of reduction in the renal substance has taken place, the concentration of urea in the blood becomes an excellent clinical index of renal failure An increase in the blood urea concentration above the normal range is then of great importance The small number of subjects in the various series which have been published and the disparity of the results obtained have led us to collect further data relating to the blood urea concentration of normal individuals

In figure 1 the series of normal blood ureas which have been reported in the literature are briefly summarized Only those groups of observations which were obtained, with two exceptions, from ten or more normal subjects and in which a reasonably reliable blood urea method was used have been included The earlier and less reliable figures have been summarized by Schwartz and McGill (7)

An examination of figure 1 shows a large degree of variation between the "normal range" and the mean values of the different groups of observations Moreover the number of observations in any single series is too small to draw any conclusions of a general nature

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During the two days and nights of observation the blood urea did not remain constant The variations which are present in the members of the group are not the same in each case or always in the same

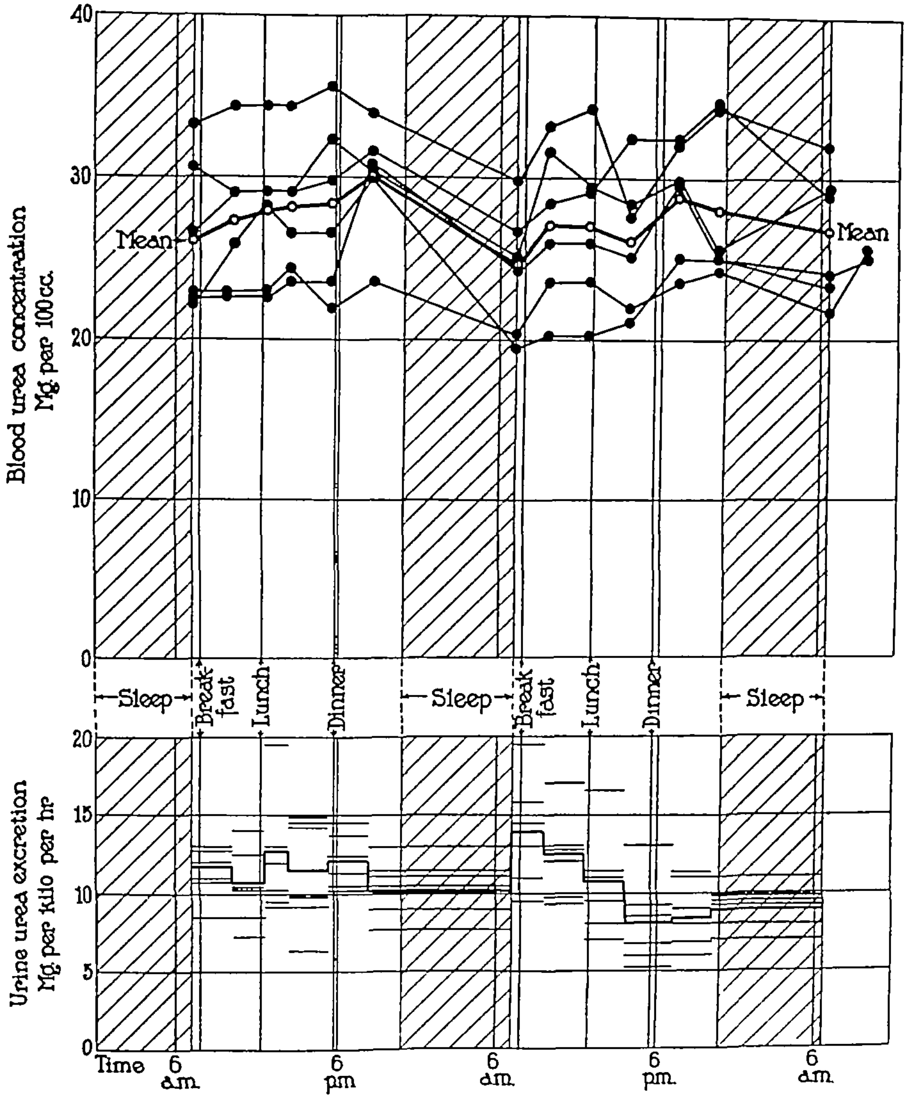

FIG 2

direction However, in the average curve an interesting variation is present which is repeated in a general way during each 24-hour period and which is supported by a large majority of the individual observa-

tions This is the undeniable tendency of the blood urea concentration to increase throughout the daytime or active hours and to fall again during the night or period of sleep In another experiment somewhat similar to this one but unsuitable for inclusion here this variation was found to be even more evident

The reason for the day rise and night fall in the blood urea is not plainly evident The ingestion of food and hence of protein during the day may contribute to the daily rise This seems probable because the most acute rise follows the evening meal (dinner) which contained the most protein It is certain that changes in the degree of renal activity are at least not primarily responsible, for the urine urea excretion is much less during the night than during the day, a finding directly opposite to that which would be expected if variation in this factor caused the blood urea variation A general examination of the various curves would seem to indicate that the variation is more dependent on changes in the general metabolic rate than any other factor The blood urea decrease during the night would then be associated with a decrease in the general metabolic processes which is known to ensue and especially with a decrease in the activity of protein catabolism It is noteworthy that the two most rapid increases in the blood urea concentration which were recorded covered periods during which the subjects engaged in several strenuous games of tennis

Although the experiment just discussed gives little reason for selecting a particular time of day for drawing blood for urea estimations, a high protein diet without doubt increases the blood urea (8) above its usual level and in the case of an individual accustomed to a large protein intake it might seem wise to draw blood before breakfast But we have found in experiments not included here that single high protein meals such as might conceivably be taken in ordinary life have only a minor effect on the blood urea concentration If on the other hand an increased protein intake (e g , 1 7 instead of 1 1 gram per kilogram of body weight such as was used in our experiment) is maintained from day to day a more important increase in the blood urea takes place The same day and night variation which we described is still present but at a new and higher urea level Since the increase is present in a comparable degree at all times little would be gained even with these individuals by taking specimens at any particular time of day

THE NORMAL BLOOD UREA CONCENTRATION

However interesting the normal daily variation in the blood urea concentration may be it is not, as has been pointed out, of such magnitude as to have much practical significance in regard to the time of day at which blood for a urea estimation is taken In collecting observations with which to establish a normal average it was therefore not deemed necessary to restrict the collection of blood specimens to any particular time By chance it happens that most of them were obtained in the forenoon A total of 278 observations were made, 58 on 47 female subjects and 220 on 114 different male subjects The youngest subject was 18 years of age and the oldest 49 years Other data pertaining to the age distribution is given in figure 4 The dis-

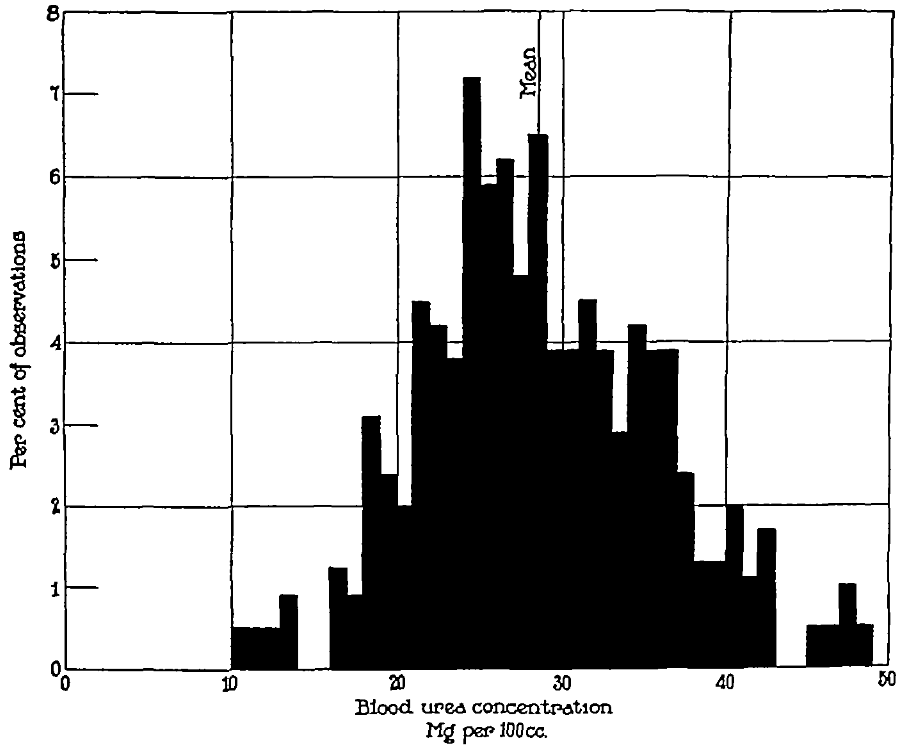

FIG 3 DISTRIBUTION OF 278 (220 ON MALES AND 58 ON FEMALES) OBSERVATIONS

tribution of the observations composes figure 3 The statistical significance of the mean value of our group of observations forms table 1

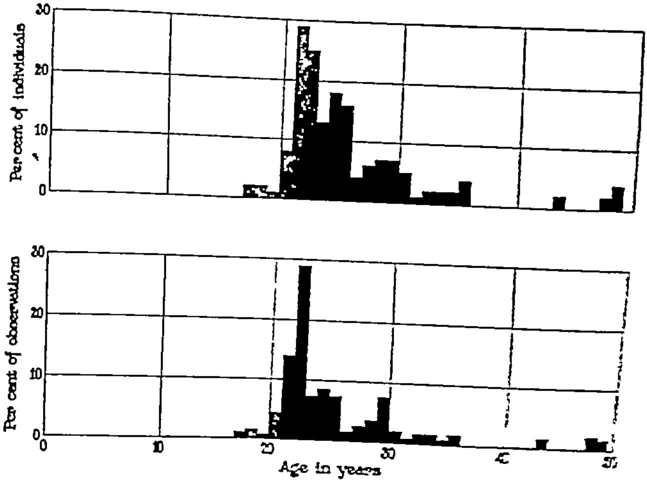

FIG 4 SOURCE OF OBSERVATIONS COMPRISING FIGURE 3

TABLE 1

Blood urea concentr[illegible] (milligrams per 100 cc. b[illegible]

	All observations	Males	[illegible]
Number of observations	278†	[illegible] *	[illegible]
High	[illegible] 0	[illegible]	[illegible]
Low	11 0	[illegible]	[illegible]
Mean Value	29.3	[illegible]	[illegible]
Standard Deviation	6 9[illegible]	[illegible]	[illegible]
Probable Error of the Average	0 2[illegible]	[illegible]	[illegible]
Coefficient of Variability	4 01	[illegible]	[illegible]

* See text.

† Two hundred and twenty observations on 114 [illegible] females.

This mean value, 29.3 milligrams of urea per [illegible] represents the normal average pretty [illegible]

the light of sex differences to be discussed shortly, have been a few milligrams lower if our observations on female subjects had been equal in number to those on males

The lowest value obtained was 11 0 and the highest 48 0 mgm of urea per 100 cc of blood Although there is a possibility, the chances are small, that any normal figures will fall outside of this range It seems safe to conclude that 50 is the upper limit of normal and that any value over this figure should be considered pathological The lower limit has not the same interest attached to it but since in certain types of renal disease the blood urea becomes lowered it is a point worthy of consideration A blood urea lower than 10 0 mgm per 100 cc of blood may be considered of questionable normality

RELATION OF THE BLOOD UREA CONCENTRATION TO SEX

As we proceeded to collect observations of the blood urea concentrations in normal individuals it became increasingly evident that female subjects tended to give lower values than males After we found that this was true the same observation was made by Klisiecki (10) who found in a short series of subjects that the figures for males were markedly higher than for females It seems worth while to offer confirming evidence on this point

Fifty-eight observations on 47 female subjects were available It was desirable that they be paired for comparison with a similar number of figures from a group of male subjects with the same age distribution In order to avoid selection in choosing the latter all of the male values for a given age were averaged and the average repeated in the comparative male series the number of times that the age appeared in the female group In figure 5 the distribution of the two groups, male and female, have been compared There can be no question that in general the blood urea concentration tends to be higher in a male than in a female subject The significance of the averages of the groups is given in table 1 The average of the male group is 35 per cent higher than the average of the female group Determined in the usual manner the probable difference between the averages is 0 66 while the observed difference is 8 60

It is generally supposed that the protein intake (per unit body weight) of males is higher than that of females Then we know (12)

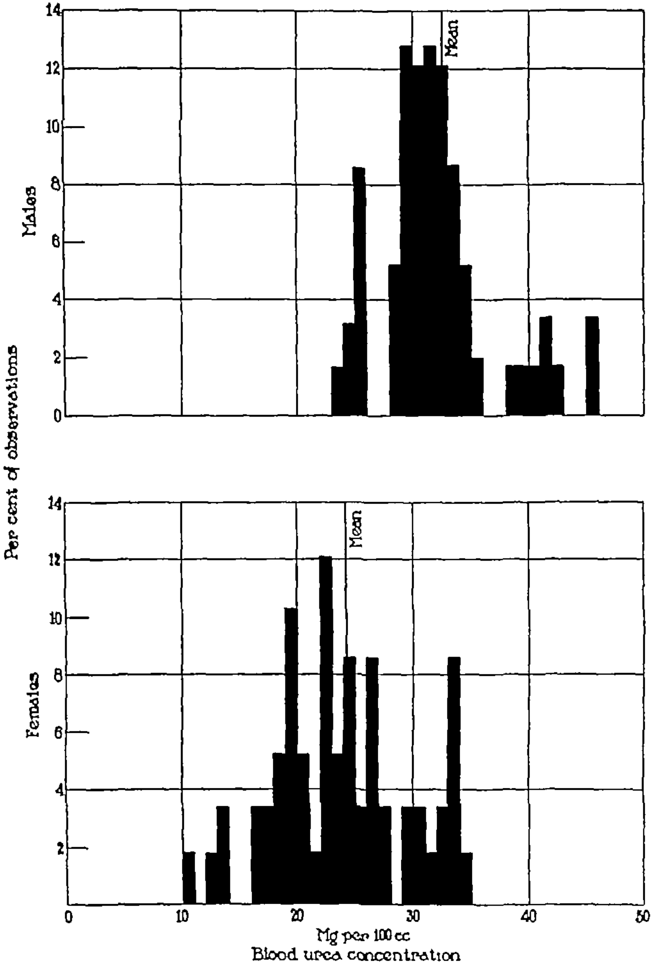

Fig 5 Fifty eight Observations from a Group of Male Subjects Compared with a Similar Number from a Comparable Group of Female Subjects

that the basal metabolic rate and therefore, probably, the rate of protein catabolism, is slightly higher (per unit body surface) in male subjects than in females of the same age These facts suggest a possible explanation of the sex difference in the blood urea which has just been noted although it may not be the correct one

RELATION OF THE BLOOD UREA TO AGE

Our observations are inadequate both in age distribution and number to determine conclusively the relation, if any, of the blood urea concentration to age There does however seem to be a tendency for the blood urea to increase with age The definite presence of a similar

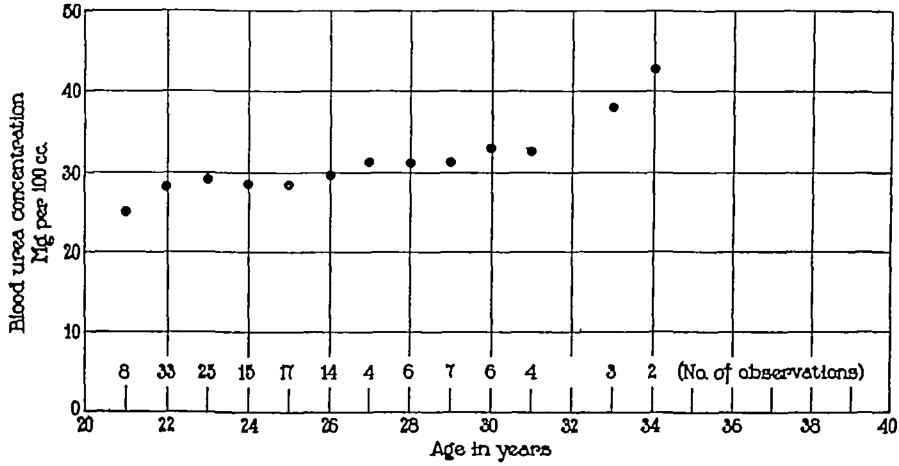

FIG 6

increase in the blood ureas of a large group of albino rats in which most of the factors could be controlled has prompted us to point out the similar tendency in our observations on man

In figure 6 have been plotted the average blood urea concentrations for groups of male subjects of various ages The curve suggests an increase of blood urea concentration with increase in age

SUMMARY

Although not of such magnitude as to be of practical significance the blood urea concentration of normal individuals undergoes a measurable fluctuation during the day and night In general the blood

urea concentration has a tendency to fall during the night only to rise again during the following day

The blood urea concentrations of a group of normal individuals were determined A total of 278 observations were made, 58 on 47 female subjects and 220 on 114 male subjects A high value of 48 0, a low of 11 0 and a mean of 29 3 mgm of urea per 100 cc of blood were found for the group The limits of the normal blood urea concentration have tentatively been placed at 10 0 to 50 0 mgm per 100 cc of blood

The blood urea concentrations of male subjects have been found to be higher than those of comparable female subjects In the male group a high value of 46 2, a low of 25 8 and a mean of 33 0 mgm of urea per 100 cc of blood were found while in the group of female subjects the values were respectively 39 0, 11 0 and 24 4 mgm of urea per 100 cc of blood The mean of the male group is 35 per cent higher than the mean of the female group

Certain results, although not conclusive, suggest that there is a tendency for the blood urea concentration to increase with age

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STUDIES ON HUMAN CAPILLARIES

IV Observations on the Nature of the Capillary Pulse in Aortic Insufficiency

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The first description of the capillary pulse was given in 1868 by Quincke (1) who observed it in a number of different conditions but stated that it was most manifest in cases of aortic insufficiency He thought that the mechanism involved was a true pulsation in the capillaries, that is to say, a pulsatile movement in the capillaries resulting from cardiac systole The phenomenon has come to be commonly recognized in clinical medicine and until recently it was assumed that it was due to actual pulsation in the capillaries Since it has been shown, however, that the capillaries can be viewed microscopically the mechanism involved has been studied by several investigators but no agreement has been reached as to its nature In conditions in which a capillary pulse is present there is apt to be a pulsatile movement of the whole part examined due to the heart beat, and as this takes place at the precise moment when the changes for which one is looking would take place, the greatest care must be observed in carrying out the observations so that in consequence of the motion involved the capillaries do not slip out of focus

Before the advent of capillary microscopy Herz (2) expressed doubt as to whether pulsation took place in the capillaries and thought rather that it did so in the arterioles As the result of his microscopic observations of the skin capillaries Jürgensen (3) differentiated two groups of cases, one with a true capillary pulse in which there was an actual pulsation of the stream within the capillaries and the other with a pseudo-capillary pulse in which there was no pulsation of the stream In the latter the impression of pulsation was given to the capillaries

of the superficial layers by pulsation transmitted to them by the pulse of deeper lying vessels such as the digital arteries and arterioles. The former he thought was most often present in aortic insufficiency and the latter was seen in many cases of arteriosclerosis. Freedlander and Lenhart (4) as the result of their studies arrived at similar conclusions. Weiss and Dieter (5) described a pulsatile flow in the capillaries in aortic disease while Secher (6), Fischl (7) and Hisinger-Jagerskiold (8) came to the conclusion that the phenomenon was not due to pulsation of the blood stream within the capillaries. Secher saw pulsation in the capillaries in a few cases of his series but Hisinger-Jagerskiold only observed it in one of his. Boas (9) studied the capillaries of the nail fold in cases of aortic insufficiency and hypertension and came to the conclusion that the capillary pulse was not a manifestation of pulsation of the capillaries but was due to an exaggerated pulsation of the arterioles and possibly of the venules of the sub-papillary plexus. Sumbal (10) investigated the capillaries of the lip in cases of aortic regurgitation and stated that pulsation could be seen in every case in the capillaries in which the flow was not too rapid. As the result of Sumbal's work Boas (11) reinvestigated the subject and studied the capillaries in various situations. He was able to demonstrate actual pulsation in the capillaries in some patients with aortic insufficiency but he did not think it was present with sufficient constancy or intensity to warrant adopting it as the explanation of clinical capillary pulsation. Lewis (12) has more recently carried out an extensive study of the question. He regarded macroscopic capillary pulsation as a physiological phenomenon which can readily be induced in normal individuals by heating the part examined and thus causing dilatation of the arterioles. He stated that anything which induces arteriolar dilatation will bring about pulsatile flow in the capillaries. He never failed to observe pulsation in the capillaries of any area in which pulsation of color was visible to the naked eye and in which the blood flow in a reasonable number of capillaries could be detected. He thinks that every case, regardless of etiology, in which clinical capillary pulsation, that is to say a change of color, is evident, shows pulsation in the capillaries due to dilatation of the arterioles. When macroscopic pulsation is observable the pulse passes from the arterioles through the capillaries

to the venules and the pulsation of these plays a greater or lesser part in the color changes observed according to the situation examined Heimberger (13) found in normal individuals that mechanical irritation of the arterial limb of the capillary or the local application of drugs which dilate them causes pulsation to appear Pulsation also resulted from light pressure on the venous limb or from heat He concluded that in normal individuals the pulse wave was most often lost in the arterial limb of the capillaries and could be seen throughout the whole capillary only when the tone of the arterial limb was reduced To summarize these statements one may say that two views are held as to the main cause of "capillary pulsation" observed in cases of aortic insufficiency (*a*) that it is due to pulsation of the blood stream within the capillaries and (*b*) that it is due to an exaggerated pulsation in the larger vessels which lie deeper

The results to be reported are based on the study of twelve cases of aortic insufficiency in which there was well marked macroscopic capillary pulsation Seven of these were of rheumatic origin, four of syphilitic and one was due to subacute bacterial endocarditis None of the cases showed marked signs of cardiac decompensation Cinematographic records of the capillaries at the nail fold and electrocardiograms (Lead II) were made simultaneously Synchronous points were recorded on the cinematographic film and electrocardiograms by means of signals which were operated by a common switch By this means it was possible to calculate the precise phase of the particular cardiac cycle to which each cinematographic photograph corresponded The details of the technique of making the cinematographic exposures and the methods employed in their study have been previously described (14, 15)

OBSERVATIONS

Changes in calibre The average size of both the arterial and venous limbs was similar to that seen in normal subjects Variations in the diameter took place continuously The extent of these changes varied from capillary to capillary in the same subject and also from subject to subject The magnitude of the variations in calibre was greater in the arterial limb in many instances than had been observed

in normal individuals (fig 1) The venous limb as a rule showed changes in diameter which corresponded more closely with the normal

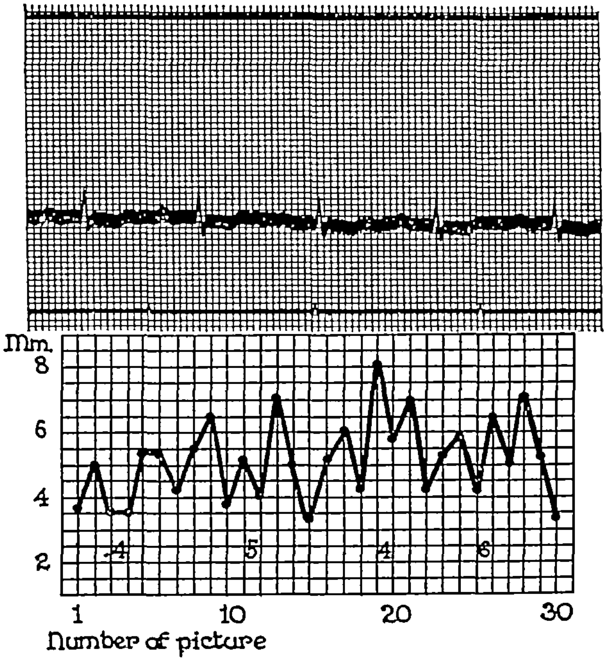


FIG 1 AN ELECTROCARDIOGRAM (LEAD II) IS SHOWN FROM A CASE OF AORTIC INSUFFICIENCY IN WHICH MACROSCOPIC CAPILLARY PULSATION WAS VISIBLE

The electrocardiogram was taken at the same time as cinematographic records were made of the capillaries at the nail fold Synchronous points of the electrocardiograms and of the cinematographic exposures were identified by means of two signals in a single circuit one recording on the electrocardiograph film and the other on the cinematograph film Underneath the electrocardiogram are shown the changes which took place in the diameter of the arterial limb of a capillary during identical cycles Each measurement is actually synchronous with the point in the electrocardiogram immediately above it without allowance for the probable transmission time

The ordinate represents the diameter of the arterial limb in millimeters at a point 2 cm from the tip of the capillary loop after magnification of the capillary 350 times. The number of cinematographic exposures was 10 per second The decimal numbers indicate the time in seconds after the onset of ventricular systole (taken as the beginning of the R-wave of the electrocardiogram) at which the maximum diameter of the arterial limb was present in each cardiac cycle

Evidences of pulsation due to the heart beat The chief interest in this investigation consists in the study of the relation of the changes

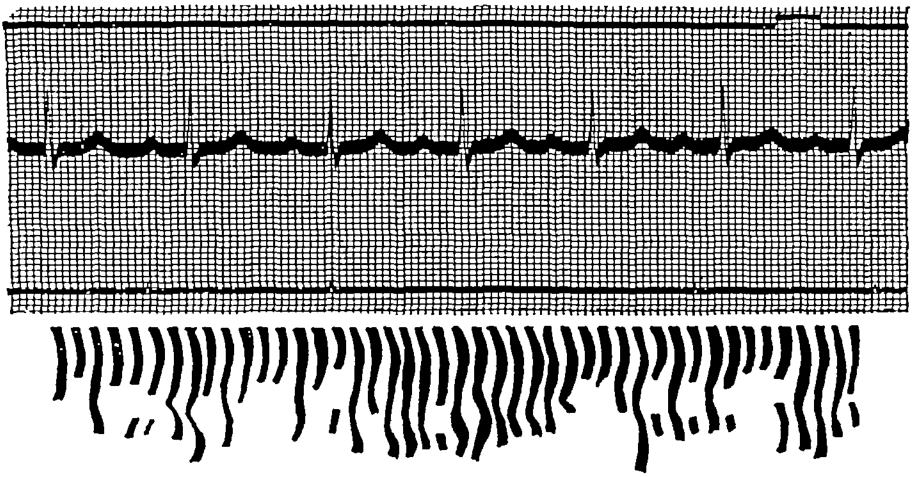
in the capillaries to the pulse beat, to see whether the capillaries show rhythmic changes in diameter such as would take place if a pulsatory flow of blood were present in the capillaries themselves Changes took place constantly in both limbs of the capillary loops but as a rule were more marked in the arterial limb These were, however, totally irregular and showed no rhythmicity such as one would expect if they were due to pulsation of the blood stream in the capillary (fig 1) If the mechanism involved were of a pulsatory nature there ought to be a constant time relation between the onset of ventricular systole—taken as the beginning of the R-wave of the electrocardiogram—and the occurrence of the maximum diameter of the arterial and possibly also of the venous limb of the capillary This time was calculated in a large number of cardiac cycles but was not constant so that no evidence of pulsation in the capillaries is afforded by this means (table 1) In a series of cycles which have been measured (table 1) the time varied in the case of the arterial limb from 0 27 to 0 71 second and in the venous limb from 0 09 to 0 71 second In one subject the flow of blood in the capillary was frequently interrupted so that the length of the arterial limb in which blood was visible varied constantly On superficial examination it looked as if

TABLE 1

The time in seconds after the onset of ventricular systole at which the maximum diameters of the limbs of the capillary loop occurred

Cycle	Arterial	Venous
	seconds	*seconds*
I	0 41	0 71
II	0 57	0 27
III	0 71	0 61
IV	0 31	0 11
V	0 30	0 40
VI	0 27	0 67
VII	0 29	0 59
VIII	0 63	0 53
IX	0 67	0 67
X	0 41	0 51
XI	0 55	0 55
XII	0 49	0 09
XIII	0 33	0 63

pulsation were present The length of the arterial limb in a large series of consecutive photographs was traced and studied in conjunction with the electrocardiogram If the changes were due to pulsation there ought to have been a rhythmic filling and emptying of the arterial limb Most blood ought to have been visible in it at a constant



0 71 0 65 0 59 0 73 0 17 0 25

FIG 2 AN ELECTROCARDIOGRAM (LEAD II) IS SHOWN FROM A CASE OF AORTIC INSUFFICIENCY IN WHICH MACROSCOPIC CAPILLARY PULSATION WAS VISIBLE

Simultaneous cinematographic records of the capillaries at the nail fold were made Synchronous points were ascertained by the technique described in figure 1 Underneath the electrocardiogram are drawings of the visible portion of the arterial limb of the same capillary in all the exposures taken when this electrocardiogram was made Each drawing is actually synchronous with the point in the electrocardiogram immediately above it without allowance for the probable transmission time.

The number of cinematographic exposures was 10 per second The drawings were made from tracings which magnified the size of the capillary 350 times The decimal numbers indicate the time in seconds after the onset of ventricular systole in each cycle at which blood was visible in the greatest length of the arterial limb

time after the onset of ventricular systole This time should correspond with that at which the heart beat produced its maximum effect in the periphery The changes seen, however, did not fulfill these expectations (fig 2, table 2) The time in seconds after the onset of ventricular systole at which the greatest length of the arterial limb

was visible differed in the cycles illustrated in figure 2 from 0 17 to 0 73 second and in those shown in table 2 from 0 01 to 0 83 second In some cycles the arterial limb was longest at the time one would expect cardiac systole to pump more blood into the capillaries, but in others this occurred at a later period and in a few just before the onset of the next ventricular contraction In many instances marked irregularity was seen during an individual cycle The type of variation is well illustrated in figure 2 In cycle I the length of the arterial limb was short at the beginning It became longer, shortened again, and was longest immediately before the next ventricular complex

TABLE 2

The time in seconds after the onset of the corresponding ventricular systole (1) at which the maximum diameter of the arterial and venous limbs occurred, and (2) at which the arterial limb exhibited its greatest length

Cycle	Arterial	Venous	Longest arterial limb
	seconds	*seconds*	*seconds*
I	0 60	0 10	0 80
II	0 51	0 21	0 01
III	0 43	0 33	0 73
IV	0 47	0 77	0 47
V	0 29	0 29	0 59
VI	0 31	0 21	0 01
VII	0 65	0 35	0 35
VIII	0 57	0 57	0 07
IX	0 27	0 27	0 67
X	0 69	0 19	0 29
XI	0 83	0 43	0 83
XII	0 21	0 11	0 21

In cycle II the limb was also very variable, being long at the beginning and also towards the end The amount of blood visible in the arterial limb in cycle III was greater than in the two previous cycles and remained approximately the same throughout Cycle IV showed a progressive decrease throughout, while in cycle V the total length remained approximately the same except once near the beginning when it became longer, at other times small gaps in the stream took place In cycle VI the limb presented a gap and then became much shorter but increased considerably at the middle and end, the length remaining about the same throughout these periods

Blood flow The capillaries at the nail fold were studied by inspection over prolonged periods of time In this condition the difficulty of keeping the capillaries under observation which has been described by previous authors is especially great as the finger usually moves with every pulse beat By careful fixation of the finger the extent of this movement can be reduced to a minimum but even then it is necessary to focus very carefully all the time in order to see the flow clearly Variations in flow took place continuously in the various capillaries In the greater number these changes bore no relation to the pulse beat and resembled those seen in normal individuals In a few, changes in the rate of flow were present for a short time which suggested pulsation but it was impossible to be sure that this was the mechanism involved

SUMMARY AND DISCUSSION

These studies show that the diameter of the capillaries in cases of aortic insufficiency was constantly changing The various capillaries differed in this respect and no two subjects were alike The blood flow also was very variable The type of change observed resembled that seen in normal individuals In several instances the magnitude of the variations in the arterial limb was greater than was seen in normal subjects and in patients with heart disease without cardiac decompensation The changes in the venous limb resembled those in normal subjects The mechanism of the production of these changes is uncertain The possible factors have been discussed in a previous paper (14) No evidence was found of pulsation in the capillaries of the nail fold although macroscopic pulsation was present in the vessels under the nail and in those behind the nail fold The site chosen for observation is not the most suitable for displaying the phenomenon but is the only one at present available with our technique It is possible that pulsation might be seen in the capillaries in a more favorable situation

CONCLUSIONS

1 The calibre of the arterial and venous limbs of the capillaries at the nail fold has been investigated by means of cinematography in 12 cases of aortic insufficiency in which macroscopic capillary

pulsation was present Simultaneous electrocardiograms were made so that the relation of the capillary changes to the heart beat could be studied

2 Variations in the diameter of the arterial and venous limbs took place continuously The changes in the arterial limb in some subjects were more marked than those seen in normal individuals but the changes in the venous limb as a rule were not so marked as in the arterial and resembled those seen in the normal

3 No evidence was present to indicate that pulsation due to the heart beat was present in the capillaries examined

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STUDIES ON HUMAN CAPILLARIES

V Observations in Cases of Heart Disease with Regular Rhythm

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In previous studies of the capillary circulation it was found that changes in the calibre of the capillaries took place continuously, both in health when the rhythm of the heart is regular, and in auricular fibrillation The extent of these changes appeared to depend on the state of circulatory compensation and was independent of the rate or regularity of the pulse Similar variations were observed in advanced decompensation both in cases of regular and of irregular rhythm The present investigation was undertaken to study the changes which take place in heart disease with regular rhythm from the early to the late stages of the disease Weiss (1) found in his studies of the capillaries in living subjects that cases of mitral insufficiency without cardiac decompensation showed a normal picture, while in the early stages of mitral stenosis a distinct slowing of the stream was observed Cases of cardiac decompensation, however, showed marked dilatation of the venous limb and the blood stream was slow and had a granular appearance These findings were in the main confirmed by Schur (2), Jürgensen (3), Neumann (4), Secher (5), Freedlander and Lenhart (6) Secher, however, described a normal capillary picture in this condition in spite of symptoms of cardiac insufficiency Hisinger-Jagerskiöld (7) studied a large number of cases of valvular and myocardial heart disease with regular rhythm He stated that cases with full compensation or with only slight decompensation did not differ from normal subjects but those with clinical signs of decompensation as a rule showed the changes described by Weiss in this condition He

further described a group of cases which showed congestion of internal organs but otherwise no clinical signs of cardiac decompensation In these the size of the loops was normal and the picture closely resembled that which the author associated with anemia

The results to be described are based on the study of eight cases of heart disease with regular rhythm, seven of which were of rheumatic origin while the other was one of chronic myocarditis These cases varied in their severity from a degree in which a heart lesion had just developed to one in which cardiac decompensation was marked Cinematographic observations of the capillaries at the nail fold and simultaneous electrocardiograms were made Synchronous points were recorded both on the photographic and the electrocardiographic films The details of taking the cinematographic exposures and the method employed in their study have been reported in previous papers of this series (8, 9) The technique used in recording synchronous points on the cinematographic and electrocardiographic films has also been described in a previous paper (10)

The size of the loops There was marked variation in the size of the loops in the same subject and differences were also seen between individual subjects The state of compensation markedly affected the size of the loops, especially the venous limb The average size of the arterial limb in early cases was from 0 014 to 0 015 mm , while that of the venous was from 0 015 to 0 016 mm In advanced cases, the arterial limb varied from 0 015 to 0 017 mm and the venous from 0 017 to 0 018 mm The early cases thus presented a picture such as had been observed in normal individuals while the advanced cases resembled that seen in auricular fibrillation with clinical signs of decompensation The values given are those of most of the loops measured, and although larger and smaller loops were studied the changes observed were similar in all

Variations in calibre Variations in the diameter of the loops of about equal extent in both the arterial and venous limbs took place in the same subject from moment to moment The magnitude of these changes varied in the loops of the same subject and also in different subjects The alterations were comparatively small, however, compared to the total breadth of the limb which remained approximately the same Their magnitude was definitely influenced by the state of

cardiac compensation In the early stages the variations were less marked than in the later stages (figs 1 and 2)

Evidence of independent contractility of the capillaries Curves which were prepared in a manner similar to those described in previous papers in this series have been studied to see whether there was evi-

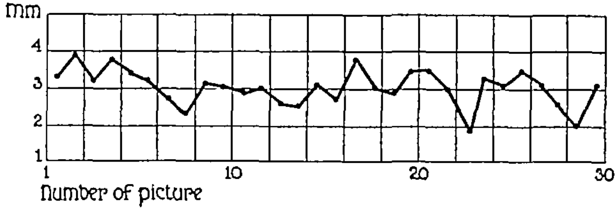

FIG 1 THE CHANGES ARE SHOWN WHICH TAKE PLACE IN THE DIAMETER OF THE ARTERIAL LIMB OF A CAPILLARY IN AN EARLY CASE OF MITRAL STENOSIS × 350

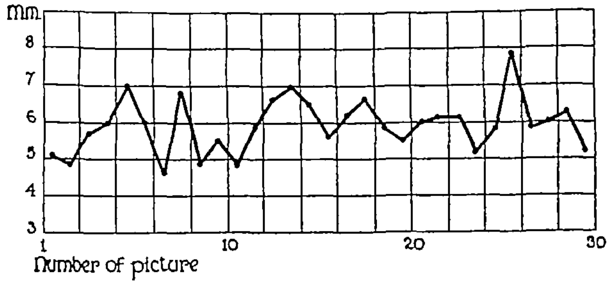

FIG 2 THE CHANGES ARE SHOWN WHICH TAKE PLACE IN THE DIAMETER OF THE ARTERIAL LIMB OF A CAPILLARY IN A CASE OF CHRONIC MYOCARDITIS WITH ADVANCED HEART FAILURE × 350

dence of a peristaltic wave of the capillaries or of local rhythmical contractions in them The changes in diameter took place irregularly and no rhythmicity was seen so that neither of these mechanisms appears to be the cause of their production

Evidence of pulsation due to the heart beat The method of recording simultaneously the capillary changes and the electrocardiogram en-

abled one to study whether any of those observed depend on pulsation on the capillary wall, due to an effect on the blood stream incident to cardiac systole The duration of each cardiac systole could be accurately measured If the changes were of a pulsatile nature the maximum diameter of the limbs of the capillary loops ought to occur at a constant time after the onset of each ventricular systole All the curves have been analyzed from this point of view but the time at which the maximum diameter occurred has no relation to the onset of cardiac systole It appears, therefore, that cardiac pulsation does not account for the changes observed

Blood flow The blood flow was studied by inspection over prolonged periods of time The rate of flow was continually changing in the same capillary, different capillaries in the same subject also varied in this respect In early cases the stream was usually rapid and resembled in every respect that seen in normal subjects In the more advanced cases the rate of flow was slower while in those with advanced heart failure the stream was very slow and in many cases stasis was present for considerable periods of time Marked sudden variations were often seen and gaps in the corpuscular stream were frequently present The general appearance was similar in every respect to that seen in cases of auricular fibrillation with advanced heart failure

Digitalis The more advanced patients were studied both before and after thorough digitalization Only one case derived definite clinical benefit In this case the extent of the variations in the diameter of the limbs of the capillaries was reduced while the blood flow improved in a corresponding manner In the other cases which were uninfluenced by digitalis there was no change observed in the capillary circulation

DISCUSSION

The variations which took place in the calibre of the capillaries in heart disease with normal rhythm were of a similar nature to those which had been observed in normal subjects Those cases which showed no clinical signs of heart failure did not differ in any respect from the normal, while advanced cases showed changes of the same nature but of greater magnitude They corresponded closely to the changes which were seen in cases of auricular fibrillation with a com-

parable degree of decompensation The extent of these variations bore no relation to the pulse rate but seemed to correspond to the state of efficiency of the circulation as judged by the clinical condition of the patient

The blood flow in the capillaries showed a similar correspondence to the state of cardiac compensation

No evidence was found of independent contractility of the capillaries nor were the changes due to a pulsatile motion conveyed to the blood stream by the heart beat Their cause is in doubt Their nature is similar to that observed in normal cases The possible factors involved have been discussed in an earlier paper (9) The differences which exist appear to depend on the power of the heart itself to maintain an efficient circulation

CONCLUSION

1 The calibre of the arterial and venous limbs of the capillaries at the nail fold has been studied by means of cinematography in eight cases of heart disease with normal rhythm

2 Changes of equal magnitude in the diameter of the arterial and venous limbs of the capillary loop take place from moment to moment The extent of these changes varies in different capillaries in the same subject, differences are also seen between individual subjects

3 The magnitude of the variations depends on the state of cardiac compensation and has no relation to the rate of the pulse

4 The changes do not appear to be due to a peristaltic wave of contraction, a local rhythmical contraction of the capillaries nor to the action on the capillary wall of a pulsatory motion of the blood stream caused by the heart beat The cause of their production is uncertain

5 The blood flow in cases without cardiac decompensation is similar to that seen in normal subjects while in cases with cardiac decompensation the flow is slow and irregular such as was observed in cases of auricular fibrillation with a comparable degree of decompensation

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I

THE MECHANISM OF THE ACTION OF IODIDES ON THE NITROGEN METABOLISM

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(Received for publication March 18, 1927)

It has been shown by a number of observers that the administration of iodides both to dogs and to human beings causes an increase in the output of nitrogen in the urine One of the earliest observers (1) working with dogs showed that this was in part at the expense of the nitrogen excreted in the feces, but that the total amount of nitrogen excreted was none the less increased We have been able to confirm this in human beings and also in the dog Iodine has been shown to have lytic effects on fibrous tissue of which this increased nitrogen elimination may be a manifestation Sollman (2) too has demonstrated this lytic action on subcutaneous nodules produced by the injection of local anesthetics Various hypotheses have been offered to explain the mechanism of this action of iodides Inhibition of antitryptic activity of the blood has been postulated by Jobling and Peterson (3) to account for the lytic action of iodine

In previous work from this laboratory it has been shown that in the human being there is an increase in the nitrogen excretion following the ingestion of iodides (4) It has been further shown that this increase does not change the nitrogen partition (5) It has been shown that the administration of sodium iodide for three days is accompanied by an immediate increase of 15 per cent in the nitrogen excretion in the urine, coinciding with the period of drug administration During this period the non protein nitrogen of the blood fell only slightly However, when potassium iodide was administered the increased excretion of nitrogen was delayed and the non protein nitrogen of the blood rose until the increased excretion began Consequently this nitrogen must come from some source in the body rather than represent simple retention due to kidney impermeability

inasmuch as the excretion continued on the same level as with sodium iodide To follow further the course of this nitrogen is the purpose of the present experiments

Our experiments were carried out on dogs which were fed a constant diet of whole wheat bread and milk The latter was made from dried milk of a known and constant composition and the fluid intake was kept constant The dogs took this diet very well, showed no diarrhea nor loss of weight It represents 2 77 grams of nitrogen per day

TABLE 1

Shows the daily twenty-four-hour urinary nitrogen output of dogs on a constant diet

The fourth, fifth and sixth days show the effect of iodide injection

Animal number	Experiment number	Day of experiment								
		1	2	3	4	5	6	7	8	9
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
1-1	1	2 0	2 2	3 1	3 0	3 4	3 7	3 6	3 0	2 6
2-1	2	2 6	3 5	2 9	5 0	4 1	5 8	3 3	5 2	5 3
3-1	3	2 3	2 1	2 8	2 1	2 6	2 7	1 7	2 8	2 3
3 2	4	2 1	1 8	2 2	1 9	2 1	1 9	1 9	1 7	1 6
3-3	5	1 8	1 9	1 8	1 7	1 4	1 8	—	—	—
3-4	6	1 8	1 7	1 6	2 2	2 0	1 6	1 2	1 5	1 5
3-5	7	1 5	1 5	1 7	1 9	1 8	—	—	—	—
5-1	8	3 0	3 2	2 7	3 2	3 1	3 0	3 1	2 4	2 4
5-2	9	3 0	2 7	3 9	3 4	4 2	4 1	3 8	3 3	3 2
6-2	10	2 3	1 5	3 0	3 4	2 6	1 4	2 7	2 2	2 0
6-3	11	2 2	2 0	2 1	2 2	3 2	1 8	1 0	1 7	2 7
7-2	12	1 3	1 2	0 9	1 2	1 3	1 6	1 2	1 4	1 4
8-1	13	2 9	1 8	3 3	3 2	3 2	2 3	2 1	1 3	1 0
9-1	14	1 6	2 0	1 9	1 5	3 8	1 4	2 2	1 1	1 8
Average.		2 2	2 1	2 4	2 6	2 8	2 7	2 3	2 2	2 3

Sodium iodide was administered in aqueous solution subcutaneously as Hesse (7) showed that the results on nitrogen excretion are the same as when it is taken per os This in itself is an indication that the liver is probably not primarily concerned in the mechanism of this action of iodides One of our difficulties was in the irritating properties of the solution The site of the injection in almost every case showed a sterile slough after a few days and evidently caused some discomfort to the animal, though we made the solution as

dilute as possible without increasing the size of the injection mass beyond reasonable limits However, the usual effect on the urinary nitrogen excretion was obtained During the period in which the wound was open we could detect no effect on the nitrogen excretion The dose administered was 100 mgm per kilogram of dog once daily for three days The total nitrogen in the urine was determined by the Kjeldahl method and total sulphur was determined by the method of Fiske (8) As soon as the dog was in positive nitrogen balance for three days the iodide was injected once a day for three days

As will be seen from table 1 fourteen such experiments were done

TABLE 2

Shows the output of total sulphur in the urine of the same animals as those shown in table 1

Iodide injection on the fourth fifth and sixth days

Animal number	Experiment number	Day of experiment 1	2	3	4	5	6	7	8	9
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
5-1	8	1 12	1 21	1 04	0 84	0 60	0 61	0 81	0 51	0 53
5 2	9	0 96	0 74	0 86	0 92	1 05	1 06	1 11	1 36	1 09
6-2	10	0 45	0 31	0 55	0 63	0 46	0 29	0 59	0 56	0 44
6-3	11	0 56	0 44	0 56	0 45	0 66	0 37	0 34	0 39	0 57
7 2	12	0 60	0 49	0 47	0 42	0 42	0 51	0 48	0 59	0 52
7 3	15	0 59	0 52	0 32	0 36	0 38	0 50	0 24	0 37	0 35
8-1	13	0 75	0 75	0 78	0 95	0 91	0 77	0 65	0 71	0 50
9 1	14	0 47	0 56	0 45	0 36	0 88	0 41	0 68	0 63	0 81
Average..		0 70	0 63	0 63	0 62	0 67	0 57	0 61	0 64	0 60

and on the average there is an increase of 27 per cent per day in the nitrogen excretion during the period in which sodium iodide was administered Working this out statistically it is found that the mean daily excretion during the three days of the pre iodide period is 2 2 $\pm$ 0 103 The mean excretion of the period of iodide administration is 2 6 grams and considering the P E of the mean of the pre-iodide period to be $2\frac{1}{2}$ times the S D , or 0 25 gram, it will be seen that this represents a real increase in nitrogen excretion dependent upon the drug alone

From table 2 it will be seen that the total sulphur excretion remains constant during this period and does not increase with the nitrogen

excretion After one or more experiments of this type had been done on the dog a thyroidectomy was attempted Hesse (7) has reported no difference in this action of iodides after the removal of the thyroid, although he states that his experiments were unsatisfactory due to the development of tetany in his dogs Of those attempted, in two animals we successfully removed the thyroid and left behind sufficient parathyroid tissue so that the dog lived without tetany The iodide injections were repeated under similar conditions

TABLE 3

Shows the daily twenty-four-hour urinary nitrogen output in the experiments after thyroidectomy

Figures in parentheses indicate the probable figure estimated from the urinary output. On most of these occasions it was observed that the animal urinated either just before or just after the moment of collection

Animal number	Experiment number	Day of experiment								
		1	2	3	4	5	6	7	8	9
		grams	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
1-2	16	3 4	3 2	3 0	1 7 (2 7)	3 7 (2 7)	3 4	2 4 (3 4)	4 3 (3 4)	2 7
1-3	17	3 6	3 3	2 9 (3 6)	4 3 (3 6)	3 7	2 7 (3 7)	4 8 (3 8)	4 0	3 8
1-4	18	2 8	2 3	4 1	—	2 6	3 4	—	—	—
6-4	19	4 3 (2 7)	2 4	2 2	0 8 (1 9)	4 5 (1 9)	0 5 (1 9)	2 1	— (2 7)	5 4 (2 7)
Average		3 5 (3 1)	2 8	3 1 (3 2)	2 3 (2 7)	3 6 (2 7)	2 5 (3 1)	3 1 (3 1)	4 1 (3 4)	4 0 (3 1)

as before thyroidectomy and under these circumstances no increase in the nitrogen excretion occurred Sulphur excretion was not determined in these experiments This is shown in table 3

The results are depicted graphically in the accompanying charts It is evident from these experiments that in dogs on a constant diet the injection of sodium iodide causes an increase in the nitrogen excretion in the urine This increase in nitrogen excretion is not accompanied by a diuresis nor by an increase in the total sulphur

excretion During the period of increased nitrogen elimination the concentration of the urine changes These effects are absent if the thyroid is removed Figure 2 shows the effect of sodium iodide on

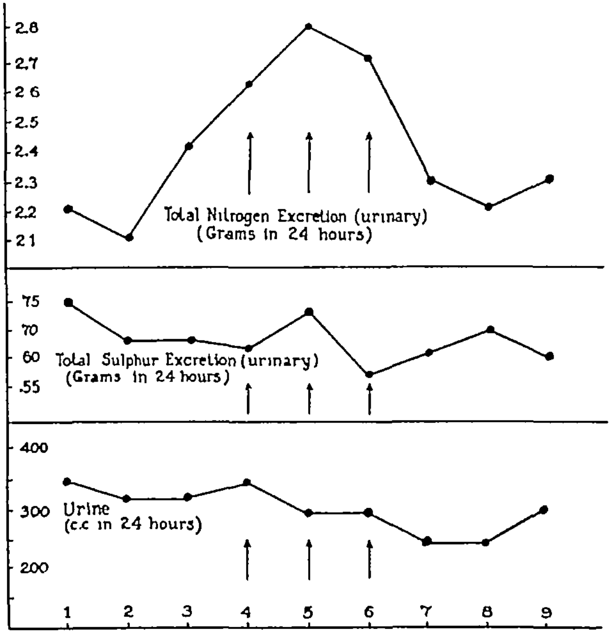

FIG 1 SHOWS THE MEAN EXCRETION OF 14 EXPERIMENTS LISTED IN TABLES 1 AND 2

Note that the output of urine remains essentially constant. The arrows indicate the three days on which the iodide was injected

the nitrogen excretion in the same animals before and after removal of the thyroid gland

The source of this nitrogen must be a matter of speculation That this is the same nitrogen described by Lusk (9) as "deposit nitrogen" which he states is "poor in sulphur" seems likely However, the existence of deposit nitrogen is still denied by some observers though

it must be admitted that there is some nitrogen stored in the body It is evident from these experiments that the thyroid must be present for sodium iodide to produce the effect described From this it may be inferred that the thyroid plays some part in the metabolism of this nitrogen This function appears to be separated from the effect

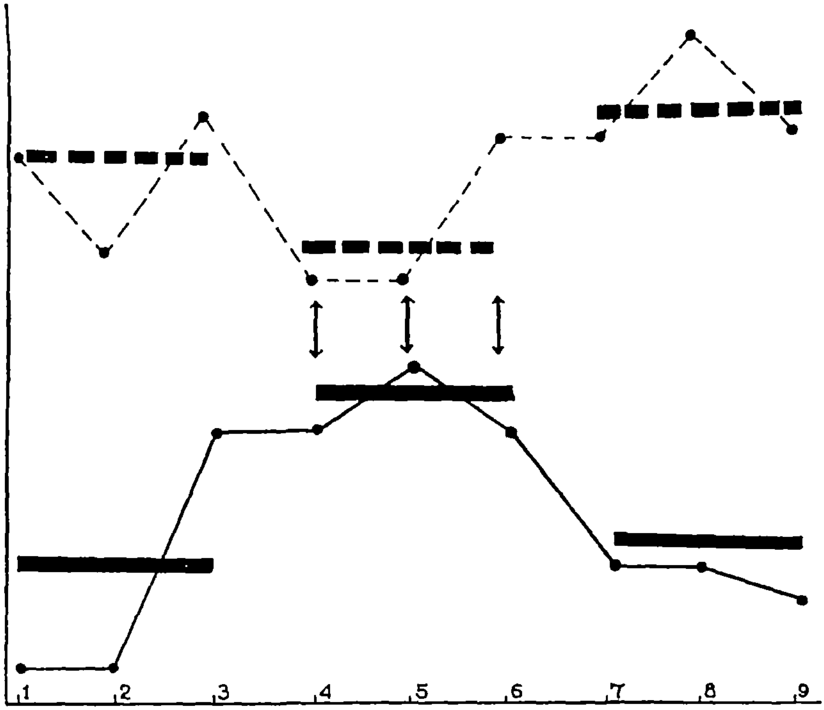

Fig 2

The upper dotted line shows the urinary nitrogen excretion of dogs after thyroidectomy The lower solid line shows the urinary nitrogen excretion of the same dogs before thyroidectomy Arrows indicate the three days of iodide administration The heavy dotted and heavy solid lines indicate the mean level of nitrogen excretion for the preiodide, iodide, and postiodide periods of three days each

of the thyroid on the basal metabolism as it has been shown (10) that iodides cause no change in the basal metabolic rate in normal subjects In certain types of hypothyroidism mucinous substances are believed to be accumulated under the skin Inasmuch as the mucins are nitrogenous substances containing no sulphur the rôle of the thyroid in these experiments seems corroborative of the findings in myxedema As soon as the occasion presents itself it is planned to check these findings by the study of a case of myxedema

SUMMARY AND CONCLUSIONS

1 A 27 per cent increase in the daily nitrogen excretion of dogs on a constant diet followed the subcutaneous injection of a solution of sodium iodide

2 This increase in nitrogen excretion was not accompanied by an increase in sulphur excretion

3 The fluid intake and urine output were both maintained on a constant level throughout these experiments

4 It seems likely that this increase in nitrogen excretion without a corresponding increase in sulphur excretion represents a mobilization and excretion of "deposit nitrogen"

5 The increase of nitrogen excretion following the injection of sodium iodide did not occur after the removal of the thyroid gland in two dogs

6 It seems evident that the presence of the thyroid gland is necessary for the mobilization and excretion of this nitrogen following the administration of iodides

7 It is suggested that the thyroid may have as one of its functions (apart from its effect on the basal metabolism) the mobilization of "deposit nitrogen" poor or lacking in sulphur

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REPEATED BLOOD SUGAR CURVES IN NON-DIABETIC SUBJECTS[1]

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(Received for publication February 24, 1927)

Various authors who have made duplicate blood sugar curves from the same individuals have considered that any lowering of the second curve was the result of the treatment or of the experimental procedure introduced The following may be mentioned as examples lowered curves in 6 patients better of arthritis (1), and in 6 of 10 patients following medication by means of vasodilator drugs, Pemberton et al (2), in 7 of 12 subjects, second curves with patients sitting which were lower than initial curves with limbs elevated, Cajorie et al (3), in four patients lowered curves accompanying reduction in weight, Labbe (4), lowered curves following arc light irradiation, Berg (5), after recovery from head injuries, Davidson and Allen (6), and when tannic acid was given with the glucose, Mertz and Rominger (7) With reference to these and other reports which might be cited, the question arises whether the reduction in the height of the second curves might be due wholly or in part to a natural tendency for the second curve to be lower than the first

Most writers have assumed that the level and the general form of the blood sugar curve of a normal individual is fairly constant from time

[1] This research was made possible through a grant by the Committee on Epilepsy, New York City This paper is no 54 in a series of studies in metabolism from the Harvard Medical School and Allied Hospitals The expenses have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of Chronic Diseases

[2] Fellow in Medicine of the National Research Council during a portion of this research

to time However, duplicate curves were found to be lower than initial curves in four of six students by Hale-White (8) and in three of five non-diabetic patients by Niemeyer (9) We have seen no reports concerning repeated curves in a large group of non-diabetic subjects

In the course of a study of blood sugar curves on 140 persons subject to recurring loss of consciousness and convulsions (10), we found that a surprisingly large proportion (24 per cent) had a high, or prediabetic type of curve In seeking to account for this, we repeated the test in a number of these individuals and found in more than half that the second or third curve was normal Because we obtained a somewhat similar lowering of duplicate curves in healthy subjects, we consider that the observation is not confined to persons with epilepsy This is a report of 50 persons in whom the blood sugar curve was repeated from one to fourteen times In all, approximately 300 curves were determined

MATERIAL AND METHODS

The subjects included five healthy persons and one patient with arthritis The others were patients with symptoms of recurring convulsions Information concerning these is contained in the previously mentioned paper (10) On initial trial, one-half of these 50 subjects showed high blood sugar curves (those which rose to above 165 mgm. and were more than 120 mgm at the end of the second hour) This proportion of high curves is double that for the whole group of 160 persons from whom this smaller group was selected, and is, of course, much higher than would be encountered in any unselected group of non-diabetic subjects Unless otherwise stated, the subjects were eating their usual mixed diet, which was not changed during the period of observation We endeavored also to keep other factors which might conceivably modify the form of the curves—such as medication, activity during the test, room temperature, etc —constant The interval between examinations varied from a few days to a number of months All tests were performed at least 12 hours after the ingestion of food For the experiments in which sugar was given by mouth, we used pure dextrose in 33 per cent solution, in an amount equal to 1 5 gram per kilo of body weight, and for the tests in which sugar was injected, we used 0 33 gram per kilo of body weight of chemically pure glucose in 20 per cent watery solution Venous blood was drawn before, and at intervals of 30 minutes, one and two hours after administration of the glucose In the intravenous tests blood was collected, in addition, four minutes after the injection

Blood was hemolized with water immediately (within 15 minutes) after withdrawal Only sufficient oxalate to prevent clotting was used Sugar was measured by the method of Folin-Wu, (11) Sugar tubes, as modified by Evans (12) were

used For the sake of brevity, we shall speak of blood sugar curves following ingestion of glucose as ingestion curves, and those following intravenous injection of glucose as intravenous curves

RESULTS

Duplicate curves A summary of the results of duplicate curves following ingestion or injection of glucose is given in table 1 Of the

TABLE 1

Two successive blood sugar curves following ingestion (50 cases) or intravenous injection (89 cases) of glucose

	Blood sugar per 100 cc.				
	Fast	4 minutes	½ hour	1 hour	2 hours
Glucose ingested					
	mgm	mgm	mgm.	mgm	mgm
First curve higher—31 cases					
Average first curve.	104		167	176	146
Average second curve.	95		146	138	116
Second curve higher—19 cases					
Average first curve	92		131	129	115
Average second curve.	97		150	148	122
Total 50 cases					
Average first curve	99		153	157	134
Average second curve.	96		147	142	119
Glucose injected intravenously					
First curve higher—19 cases					
Average first curve	94	238	165	115	99
Average second curve.	92	221	132	97	83
Second curve higher—10 cases					
Average first curve	83	226	106	84	79
Average second curve	95	237	139	97	88
Total 29 cases					
Average first curve.	91	234	144	105	92
Average second curve	93	235	134	97	85

50 duplicate ingestion curves, 31 or 62 per cent were lower and 19 or 38 per cent were higher than the initial curves Of the 25 curves which were abnormally high on first trial, 21, or 84 per cent, were lower on second trial For the whole group of 50 persons in whom duplicate curves were drawn, the second curve was distinctly lower than the first (fig 1)

Table 2 gives the measurements concerning the 31 subjects in whom the second curves were lower than the first In some the difference was negligible, in others, such as the 11 duplicate measurements shown in figure 2, it was marked The initial curve of many of these individuals was clearly abnormal—whereas the second curve was normal Cases numbers 1, 2 and 3 in table 2 and figure 2 were male students with no evidence of disease on physical examination Number 4 had chronic arthritis In addition to

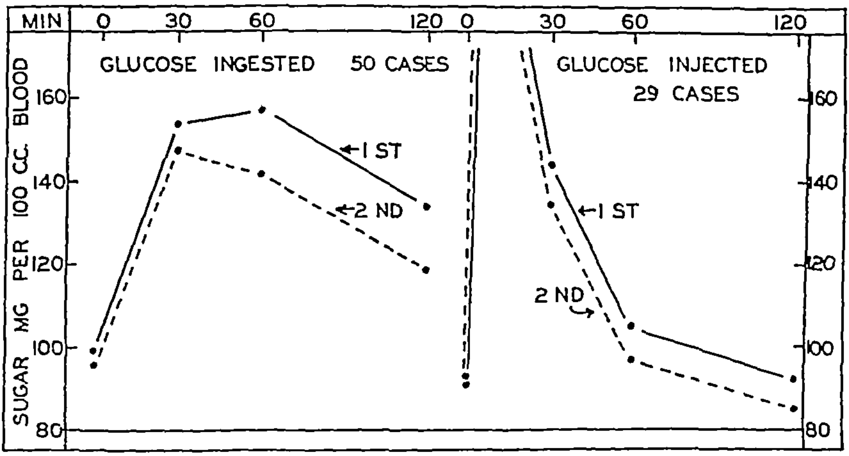

Fig 1 Average Duplicate Blood Sugar Curves of 50 Subjects Who Ingested Glucose and of 29 Subjects in Whom it was Injected

With both methods, second curves were lower than first In this and other charts, ordinate represents concentration of sugar in the whole blood and abscissa represents minutes First blood was drawn with the subject fasting, and one-half, one and two hours after the administration of glucose The four-minute values for injection curves are omitted

epilepsy, number 7 had essential hypertension, and number 14 a strong family history of endocrine disease The other patients presented no evident cause for the high initial curve which many of them showed Although the successive composite curves, as shown in figures 1 and 3, present the same shape, the configuration of many of the individual successive curves was very different.

Beeler, Bryan, Cathcart and Fitz (13) have criticized the blood sugar curve test as ordinarily performed (following the administration of

TABLE 2

Thirty-one subjects whose second blood sugar curve was lower than the first

Subject number	Blood sugar per 100 cc. of blood								Days between tests
	First curve				Second curve				
	Fast	½ hour	1 hour	2 hours	Fast	½ hour	1 hour	2 hours	
	mgm	mgm	mgm.	mgm	mgm.	mgm	mgm	mgm.	
1	123	133	148	165	109	130	137	100	7*
2	141	195	174	125	102	156	127	100	7
3	94	163	188	129	99	135	95	75	18
4	94	168	182	186	93	149	175	128	1
5	101	112	181	142	94	108	114	143	25
6	87	192	171	102		107	144	94	35
7	121	211	286	164	79	131	208	135	275‡
8	88	152	144	132	90	127	135	137	63†
9	89	156		222	90	146	190	150	295†
10	89	151	147	108	89	148	110	90	48†
11	131	152	165	108	97	125	114	100	155
12	91	156	154	114	104	132	91	80	160
13	95	145	146	133	85	100	81	91	175†
14	97	210	194	164	79	187	169	143	312†
15	100	202	203	161	100	235	190	105	97
16	125	185	222	91	107	165	186	152	260*
17	92	144	154	171	82	119	110	103	17*
18	133	182		211	92	129	114	90	130*
19	115	164	205	148	105	172	153	128	107
20	100	144	160	137	91	138	138	131	7
21	94	179	143	133	87	118	95		102*
22	101	190	200	130	95	180	179	143	15
23	100	174	198	186	99	142	149	147	4
24	92	241	241	172	92	206	136	139	41
25	98	155	181	138	91	170	117	106	14
26	145	147	176	127	105	210	178	91	45*
27	97	129	129	118	93	145	106	104	188*
28	95	154	129	98	117	122	111	100	37†
29	100	200	129	121	84	138	113	91	295†
30	102	126	185	185	100	130	153	120	28*
31	88	153	165	204	93	116	160	171	7

* An intravenous test was done in the interval.

† Two intravenous tests were done in the interval.

‡ Three intravenous tests were done in the interval

glucose by mouth) because variable speed of absorption of glucose from the gastro intestinal tract may seriously modify the degree of hyperglycemia On this account, various writers have recommended

the administration of glucose by intravenous injection We have performed comparative blood sugar curve tests following both ingestion and injection of glucose in 100 subjects The data obtained will be presented elsewhere (14) It is sufficient for our purpose here to point out that of 29 subjects in whom duplicate intravenous curves

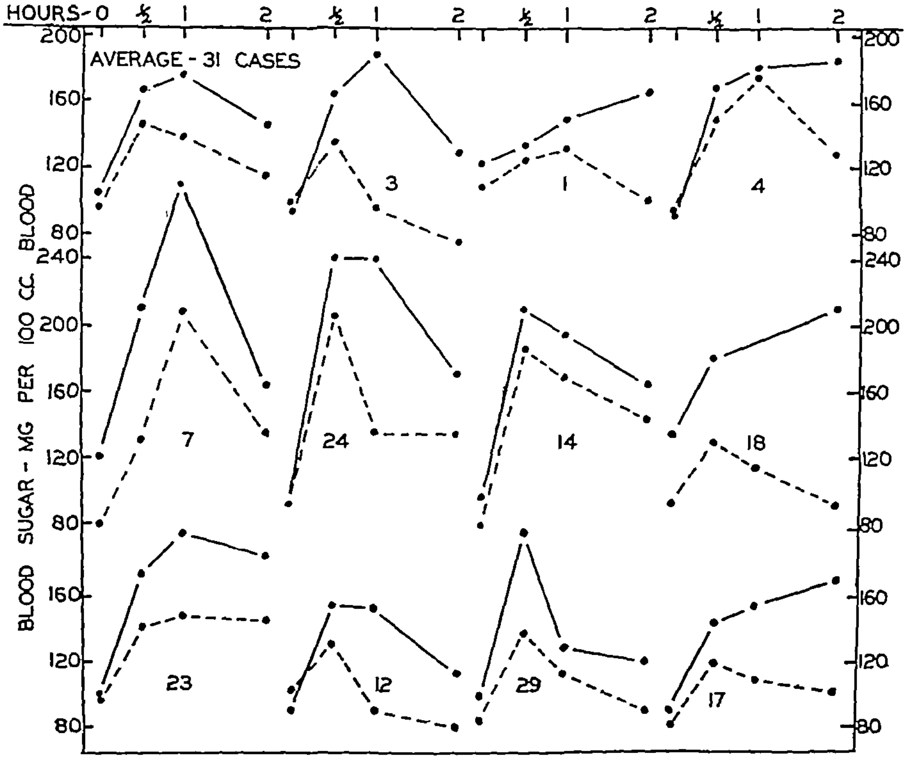

FIG 2 FIRST AND SECOND BLOOD SUGAR CURVES FOLLOWING INGESTION OF GLUCOSE IN 11 OF THE SUBJECTS NAMED IN TABLE 2

The numbers on the chart refer to case numbers in table 2 The first curve given is the average of first and second curves for the 31 subjects in whom second curves were lower than first

were drawn, the second curve was lower in 65 per cent For all 29 subjects the average second curve was distinctly lower than the first (Table 1 and figure 1) The evidence is somewhat complicated by the fact that the majority of the subjects were used for the plotting of both ingestion and injection curves and, as indicated in table 2, intra-

venous and postprandial curves were oftentimes interspersed However, individuals who showed most marked differences between first and second curves were not necessarily those in whom a test by a different method had been performed in the interval

Triplicate curves Table 3 presents the results with the 25 subjects in whom sugar curve tests following ingestion of glucose were done three times All but one of the subjects in table 3 were patients Examination of the table and inspection of figure 3 shows progressive lowering of each successive curve This is seen also in the 12 subjects in whom three intravenous curves were performed Differences

TABLE 3

Three successive blood sugar curves following ingestion (25 cases) or intravenous injection (12 cases) of glucose

	Blood sugar per 100 cc.				
	Fast	4 minutes	½ hour	1 hour	2 hours
Glucose ingested—25 cases					
	mgm	mgm	mgm.	mgm	mgm
Average first curve	101		162	166	139
Average second curve	95		155	151	126
Average third curve	100		150	140	119
Glucose injected intravenously—12 cases					
Average first curve	93	228	158	116	103
Average second curve	91	253	151	105	87
Average third curve	101	241	142	101	83

between successive injection curves were not as great as between successive ingestion curves It is to be remembered that the amount of glucose injected was only slightly more than a fifth of the amount ingested

Quadruplicate curves Table 4 shows the average results for the 15 subjects in whom four curves were made following the ingestion of glucose In contrast with the preceding observations, there was in this group no change in level of the successive curves, except that the third curve was lower than the other three The explanation for the continued high curves in this group of subjects is that these more frequently repeated tests were performed on the persons whose third

sugar curve was not normal Most of the members of this group showed a persistently high curve no matter how often the test was repeated The significance of this will be discussed later

Possible causes for reduction of curves In seeking to account for the progressive reduction in the degree of hyperglycemia which many of these subjects showed, various possible explanations need to be considered

1 Increased speed of absorption of glucose from the gastro-intestinal tract may be a factor Against this possibility is the fact that pro-

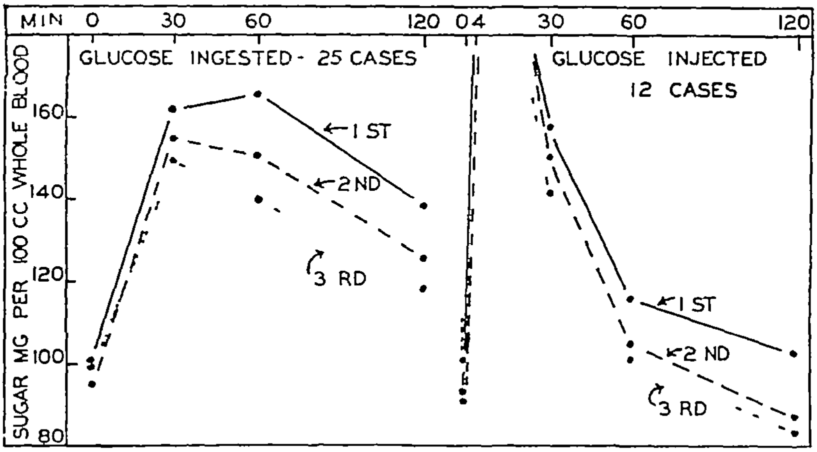

FIG 3 AVERAGE TRIPLICATE BLOOD SUGAR CURVES OF 25 SUBJECTS WHO INGESTED GLUCOSE AND OF 12 SUBJECTS IN WHOM IT WAS INJECTED

Each curve is lower than its predecessor

gressive lowering of the curve accompanied successive intravenous injections as well as successive ingestions of glucose

2 Because most of the subjects were epileptics under treatment, the increased ability to dispose of glucose introduced into the body may be a phenomena concerned with epilepsy or may be an expression of improvement in the physical condition of patients Such explanation would not hold for the three healthy students and the one subject with arthritis shown in figure 2 and table 2 (cases 1, 2, 3 and 4) In these subjects the interval between tests was from one to eighteen days, during which time no change was made in the diet or manner of living Many patients, moreover, who exhibited progressive lowering

of blood sugar curves, showed no appreciable change in their physical condition

3 It is possible that initial curves of healthy subjects and of patients alike were higher because of excitement over the first test, with accompanying increased output of adrenalin and consequent increase in the concentration of circulating glucose We were not able, however, to correlate initial high curves with any apparent evidence of nervousness on the part of subjects The three students mentioned, cases 1, 2 and 3, although evidently nervous at the first trial, were still more so at the second, as they had been told that the first test showed possibility of latent diabetes

Still more important is the evidence furnished by the subjects whose successive ingestion curves are presented in figure 4 Patient number

TABLE 4

Four successive blood sugar curves following ingestion of glucose (15 cases)

	Blood sugar per 100 cc.			
	Fast	½ hour	1 hour	2 hours
	mgm	mgm	mgm.	mgm
Average first curve	98	157	164	135
Average second curve.	95	155	161	135
Average third curve.	100	149	139	121
Average fourth curve.	95	156	165	130

7 was a young woman of 22 years who, in addition to infrequent, slight epileptiform seizures, had essential hypertension For a period of six weeks before the initial sugar curve test was performed, she was the subject of experiments which required almost daily venesection During the period of 20 months in which five ingestion and four intravenous curves were determined, her physical condition did not change materially, but her sugar curve became progressively lower (hypoglycemia in place of hyperglycemia at the end of two hours) and also showed marked alteration in configuration (the peak of the curve at the half hour rather than at the hour) The second half of figure 4 represents the successive curves of one of us who had been the subject of experimental procedures on many previous occasions Although the configuration of successive curves was constant, the last four curves were lower than the first two

4 The fourth possibility which needs to be considered is that sudden flooding of the body with pure glucose stimulated the glucose utilizing mechanism of the body to such an extent that on subsequent occasions glucose was disposed of with greater speed Because periods of weeks or months intervened between successive tests, this conception would seem improbable The sugar utilizing mechanism of the body would hardly "remember" a stimulus for so long a period of time Such an explanation, however, has certain supporting evidence which will be presented

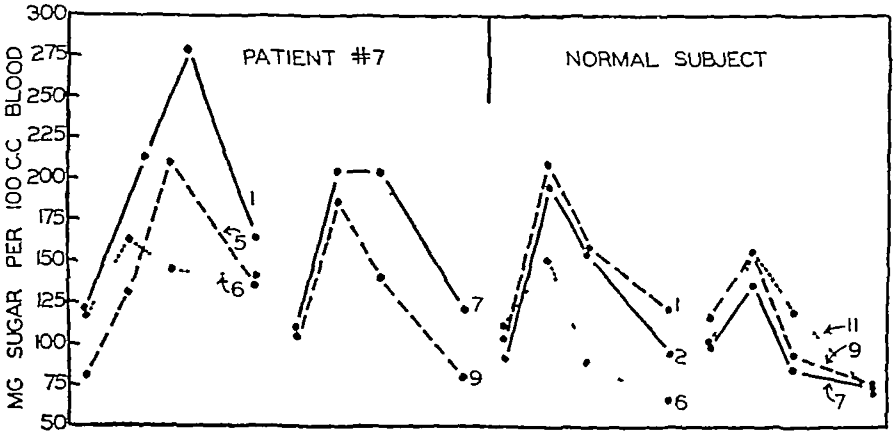

FIG 4 SUCCESSIVE BLOOD SUGAR CURVES FOLLOWING INGESTION OF GLUCOSE

Observations covered a period of 20 months for patient number 7, and of 30 months for the normal subject In both of these individuals the psychic factor as a possible cause for initial high curves could be ruled out The numbers attached to each curve indicate the chronological order in which the tests were made Absent numbers represent curves made by the intravenous method

It is well known that ingestion of a second quantity of glucose an hour or two after a first may not result in any increase in the concentration of glucose in the blood Concerning this point we have additional data which will be presented elsewhere (15) This excessive speed in the utilization of glucose is best explained by the stimulating effect of the first dose of glucose on the sugar regulating mechanism In addition to this evidence that glucose acts as a stimulus to the pancreas, we have evidence concerning the effect of lack of such stimulation during fasting

Sugar curves during fasting During fasting, as is well known, concentration of sugar in the blood is at a constant low level Available glucose is insufficient to provide for complete combustion of fat and ketosis results One would expect that if glucose were introduced into the body during starvation, it would be very quickly oxidized Strangely enough, the opposite condition is true Ingestion of glucose during fasting results in prolonged hyperglycemia This has been shown for human subjects by Staub (16), Traugott (17), Pemberton (1) and Severinghaus (18) and for rabbits by Vigneaud and Karr (19) The last named authors found that there was delay in the disappearance from the blood stream of injected as well as of ingested glucose So far as we are aware, the cause for this hyperglycemia has not been demonstrated There are two factors which especially deserve consideration First, it is possible that the acidosis of starvation may interfere with the utilization of ingested glucose Glucose is less easily oxidized in an acid medium Henderson (20) has recently emphasized the intimate relationship between the glucose and the acid-base equilibrium of the blood Second, it is possible that during a fast the decreased metabolism of carbohydrates may fail to provide the sugar disposing mechanism of the body with the stimulation it needs so that glucose which is subsequently introduced is not quickly utilized The following charts give evidence which supports the latter view

Figure 5 presents various sugar curves made with reference to fasting and changes in the alkalinity of the blood In each of the three patients the curve made during a fast was diabetic in type In each there was lack of correlation between the height of curves, and the degree of acidosis, as measured by the plasma bicarbonate For example, patient 51, whose plasma bicarbonate measured 68 volumes per cent, reacted to an initial ingestion of 100 grams of glucose with hypoglycemia At the end of a 12 day fast, his plasma bicarbonate was nearly normal (61 volumes per cent) yet two hours after ingestion of glucose his blood sugar was 240 mgm Patient 53 was given large doses of ammonium chloride for a period of two weeks This produced marked acidosis (plasma bicarbonate 44 volumes per cent) Her blood sugar curve, however, was normal and much lower than before acidosis was induced The patient was then fasted for 17 days, at the end of which time her sugar curve was diabetic in type. At this

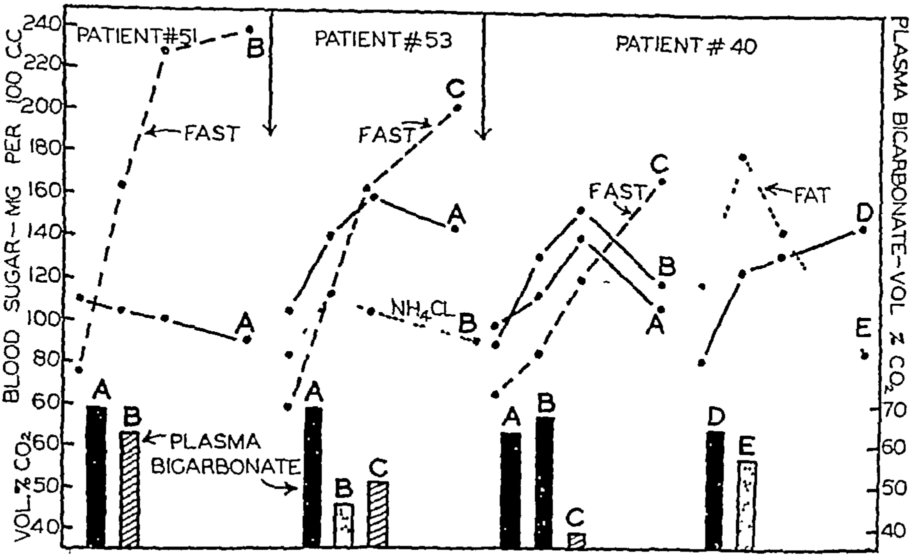

FIG 5 BLOOD SUGAR CURVES MADE DURING FASTING WITH REFERENCE TO THE DEGREE OF ACIDOSIS PRESENT

The columns at the bottom of the chart indicate the level of plasma bicarbonate (CO_2 combining power of the plasma) at the time the sugar curve was started Measurements made during a fast are indicated by broken lines and hatched columns, and those made during acidosis induced by ammonium chloride or ketogenic diet by dotted lines and columns

For patient 51, curve A was made before the fast Curve B was made after ten days of fasting, and one day in which 60 grams of intarvin and one day in which 135 cc of 40 per cent cream was given

For patient 53, curves A and B were drawn when the patient was eating a mixed diet Curve B was made after a period of 19 days in which from 5 to 20 grams of ammonium or calcium chloride had been given daily Curve C was drawn at the end of 17 days of fasting, and 24 hours after the adrenalin test shown in figure 8 It will be noted that although acidosis was greatest following administration of the acid forming salts, (44 volumes per cent CO_2) the curve made at that time was normal

For patient 40, curves A and B were made at intervals of a week before the fast, and curve C on the sixth day of the fast Another test attempted on the fourteenth day was unsuccessful because the glucose was vomited Curve D was made after one day in which 100 cc of orange juice had been drunk, and curve E two weeks later at the end of 14 days of ketogenic diet Although acidosis was greater with the fat diet than after a day of fruit juice following the 14-day fast, hyperglycemia was much less prolonged

time acidosis was less than when ammonium chloride was used (Plasma bicarbonate 51 volumes per cent) Patient 40 showed a high curve (curve C) during fast, following which she was on a high calorie, fat diet for two weeks Curve E, made at the end of this time, was not abnormally high, though ketosis was greater than at the end of the fast, when curve C was made

Further evidence is presented in figure 6 This figure shows successive sugar curves made at intervals during a fast of patient 38 These curves were made following ingestion of 10 grams of glucose, an amount sufficient to produce increase in blood sugar, but not sufficient to produce hyperglycemia or noticeably to effect the degree of ketosis, Inspection of figure 6 shows that the height of the sugar curves increased with the progress of the fast The degree of acidosis, on the contrary, was greatest on the sixth day, after which it declined We have shown elsewhere (21) that the peak of fasting acidosis, as measured by plasma bicarbonate, occurs between the third and seventh days of fasting The curves in figure 6, as well as those given by Vigneaud and Karr, (19) demonstrate that the height of curves increases progressively with the length of the fast We determined blood sugar curves during fasting in five subjects The smallest reaction obtained was in the case of a patient who at the end of a 14-day fast had measurements of blood sugar while fasting and ½, 1 and 2 hours after glucose as follows 96, 172, 186 and 165 mgm Corresponding measurements two months later were 93, 114, 95 and 97 The fact that glycemia was not greater at the end of the fast may perhaps be explained by the fact that during the fast the patient received 54 grams of thyroid extract. The consequent increase of metabolism may have partially maintained stimulation of the sugar disposing mechanism

Adrenalin sugar curves during fasting We were interested to determine whether hyperglycemia during fasting would result if the glucose was drawn from body stores Figure 7 presents various curves on two patients Patient 52 showed an increase of 22 mgm in the concentration of blood sugar following injection of adrenalin on the eighth day of a fast. Several months later, when she was on normal diet, the test was repeated At this time, although she gave pronounced symptoms of adrenalin reaction, there was almost no rise in blood sugar With patient 40 the story was somewhat different

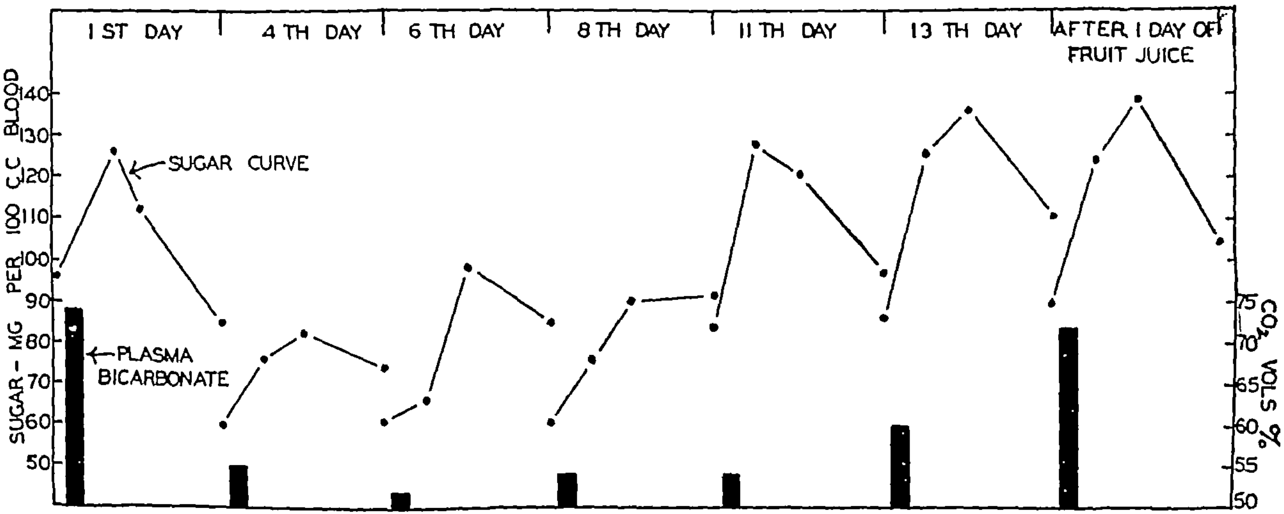

FIG 6 SUCCESSIVE BLOOD SUGAR CURVES FOLLOWING INGESTION OF 10 GRAMS OF GLUCOSE DURING THE FAST OF PATIENT 38

It will be seen that successive curves increase in height with the progress of the fast and bear no relationship to the degree of acidosis present, as measured by the amount of plasma bicarbonate On the ninth and tenth days 150 grams of intarvin were ingested daily, and on the eleventh and twelfth days 110 cc of 40 per cent cream The ingestion of this amount of intarvin, which was sufficient for caloric requirements, was not accompanied by appreciable decrease in ketosis

The increase in blood sugar following injection of adrenalin, when eating a mixed diet (curve A), was about equal to that which took place on the eleventh and fourteenth days of a fast Three curves were drawn subsequent to the resumption of food the first (curve D) after two days of orange juice, the second (curve E) after three weeks

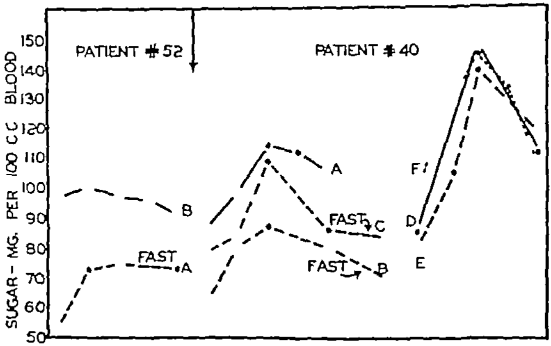

FIG 7 BLOOD SUGAR MEASUREMENTS AT HALF HOUR INTERVALS FOLLOWING THE INJECTION OF ADRENALIN

Patient 52 was given subcutaneous injections of [illegible] grain adrenalin Curve A was drawn on the eighth day of the fast, (plasma bicarbonate 42 6 volumes per cent) curve B several months later, (plasma bicarbonate 60 4 volumes per cent) The patient during the last test showed marked adrenalin reaction, although blood sugar did not rise Six curves were drawn for patient 40, following the injection of 0 5 cc. adrenalin Curve A was made before the beginning of the fast, curve B on the eleventh day and curve C on the fourteenth day of the fast Curve D was drawn following the fast and after two days in which only orange juice was ingested, curve E after two weeks of fat diet, and curve F after several months of mixed diet Measurements for plasma bicarbonate in volumes per cent of CO_2 at the beginning of various curves were as follows A 68 5, B 44 6, C 40.2, D 63 6, E 57 1

of ketogenic diet, and the third (curve F) after six months of normal diet These three curves were of the same height The fact that they were higher than the prefasting curve A may possibly be explained by the fact that preceding the determination of curve A, the patient for many months had been on a low carbohydrate diet, for which reason glycogen stores may have been depleted

Figure 8 shows contrasting curves following adrenalin injection in patient 53 The concentration of blood sugar two hours after the injection on the sixteenth day of a fast was 75 per cent above the preinjection level, against a 25 per cent increase while not fasting

In view of the acute need of the body for glucose during starvation, it is of interest that injection of adrenalin so readily called forth additional glucose We have no means of knowing the extent of the

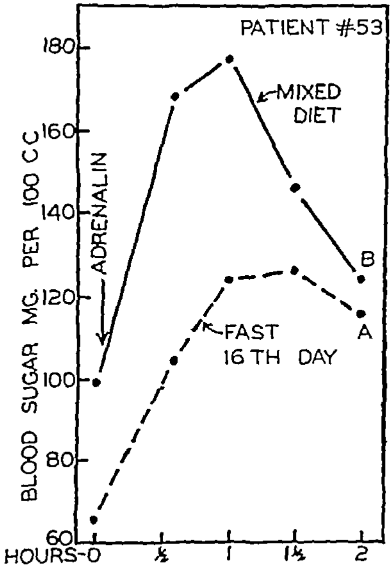

Fig 8 Blood Sugar Curves of Patient 53 Following the Injection of $\frac{1}{60}$ Grain of Adrenalin

Curve A was made on the sixteenth day of the fast, curve B several months later Two hours after the injection, blood sugar was 75 per cent above the fasting value in curve A and 25 per cent above the fasting value in curve B

glycogenolysis Presumably, it was less during the fast than during feeding, yet the hyperglycemia following adrenalin injection was as great or greater during the fast

These observations concerning blood sugar curves during fasting are not extensive enough to permit examination of factors other than the two mentioned It would seem evident that of these two factors, acidosis plays only a subordinate rôle, and that the undue hyper-

glycemia which follows ingestion of glucose during a fast may be explained by the previous diminution in stimulation of sugar disposing mechanism Vigneaud and Karr (19) suggest this but discount the influence of hyperglycemia because in one of their experiments, in which hyperglycemia had been produced 18 hours earlier by administration of morphine, ingestion of glucose was followed by prolonged increase of blood sugar whereas in another experiment, in which there had been previous injection of adrenalin, ingestion of glucose was not followed by such an increase In our experience, previous single injection of adrenalin or ingestion of food did not prevent the appearance of hyperglycemia though such increase presumably would have been greater if previous hyperglycemia had not been produced Curves did not become normal until several days after the end of a fast In several instances (see fig 7, patient 40, curve D) three to six days after a fast patients presented a steeple type of curve, with a very high peak (up to 500 mgm) at the half hour period In other instances, as seen in figure 10, the sugar curve gradually assumed its prefasting form

We have no evidence to show whether the delay in the removal of excess sugar from the blood is due to delayed entrance into the tissues, to deficient oxidation or to delayed glycogen formation Presumably, the last named factor is the most important.

Although the degree of hyperglycemia observed when sugar is fed to a fasting person is striking, such increase of sugar in the blood represents but a small fraction of the amount ingested Take for example the experiment with patient 51, shown in figure 5 After 12 days of fasting, he ingested 100 grams of glucose At the end of one hour the increased amount of oxygen consumed would account for the oxidation of approximately 2 grams of glucose, the increase of 150 mgm of glucose per 100 cc of blood would account for approximately 10 grams. Of the remaining 88 grams of glucose, a portion remained in the stomach or intestines or had entered the tissues but presumably the larger part had been deposited as glycogen in the liver and the muscles

Evidence concerning over stimulation Thus far we have presented evidence indicating that alimentary hyperglycemia may be due to the lack of previous stimulation of the sugar-utilizing mechanism, a con-

dition which may be corrected by administration of glucose On the other hand, the persistently high sugar curves of some of the subjects may represent previous over-stimulation of the pancreas Figure 9 presents nine successive ingestion curves of patient 34, a woman who showed no evidence of diabetes unless an increase of 28 pounds in weight during the period of observation may be so considered It will be seen that with two exceptions successive curves were of similar

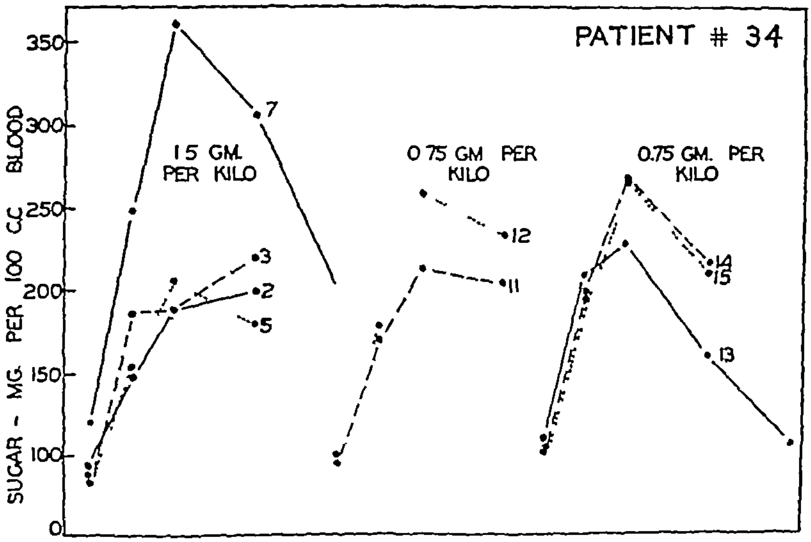

FIG 9 REPEATED BLOOD SUGAR CURVES OF PATIENT NUMBER 34, FOLLOWING INGESTION OF GLUCOSE

The amount ingested for the last 5 curves was one-half the standard amount Curve 7 was drawn the day after Christmas and curve 13 after several months of low carbohydrate diet The period of observation covered 30 months, during which time the patient's weight increased from 155 to 183 pounds

form and height The highest curve, number 7, was obtained on the day following Christmas, when she had partaken largely of sweets The lowest curve, number 13, was obtained following a four month period during which no glucose tests were performed and during which the patient was kept on a low carbohydrate diet This observation is similar to some reported by John (22) Figure 10 represents successive curves of patient number 38, whose blood sugar curves were high, but who had no symptoms of diabetes The curves under A were

obtained in a period of two weeks before fast was begun B was obtained on the thirteenth day of a fast, and C on the third day after resumption of food In addition to a mixed diet, the patient was then given 10 units of insulin twice daily for four days On the fifth day curve D was obtained This curve is very much flatter than any other Six weeks later, during which time the subject was on his normal diet,

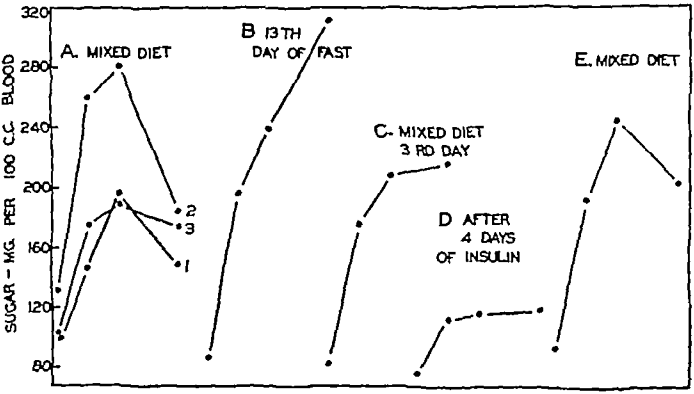

FIG 10 REPEATED CURVES OF PATIENT NUMBER 38 SHOWING CONTRASTING EFFECT OF FASTING AND INSULIN

Curves 1, 2 and 3 of A were obtained within a two-week period before the fast, curve B after 13 days of the fast which was complete except for the administration of 10 grams of glucose at intervals and of intarvin and cream, as stated under figure 6 Curve C was drawn following the fast after 3 days of mixed diet and curve D 5 days later after 4 days in which 10 units of insulin had been given night and morning and 18 hours after the last dose of insulin Curve E was made 6 weeks later

the curve was at its prefasting level The contrast between curves B and D is striking Evidently, stimulation of the sugar-utilizing mechanism was decreased by fasting and increased by previous use of insulin Though these data are not extensive, they suggest that factors which partially rest the sugar-disposing mechanism in persons whose mechanism is incompetent (either because of inherent weakness or because of previous over-stimulation) result in lowering of the

blood sugar curve, but that disuse of such mechanism, as in fasting, causes temporary increase in the blood sugar curve

The question remains whether, as Maclean and de Wesselow (23) suggested, the hyperglycemia in itself is the stimulator of the sugar-utilizing mechanism Certain of our observations would make it seem probable that the matter should be stated more broadly Probably the metabolism of carbohydrates rather than the simple presence of excess glucose in the blood is the factor of importance In favor of this is the apparent increased rate of removal of glucose from the blood following the administration of thyroid extract and of insulin It is possible, moreover, that protein, as well as carbohydrate metabolism, is concerned Though Nord (24) obtained marked hyperglycemia following injection of certain amino acids, Bertram (25) has reported that the hypoglycemic action of insulin is enhanced by mixing it with various proteins Vigneaud and Karr (19) found that feeding of protein even more than feeding of glucose increased the rate of removal of glucose in fasting Finally, the factors which favor reduction of fasting postprandial hyperglycemia are curiously like the factors which we (26) have found to favor reduction of fasting hyperuricacidemia

DISCUSSION

The data which have been presented would seem to make it clear that repeated blood sugar curves of persons with an initial high curve demonstrate two classes of individuals The first and smaller group consists of those whose sugar-disposing mechanism has been over stimulated and whose blood sugar curves remain high or tend to become higher with successive tests These persons presumably comprise the group from which diabetics are to be recruited The second and larger group consists of those who present an initial high curve which tends to become progressively lower with repeated tests These persons would seem to have a competent sugar-disposing mechanism which only needs adequate stimulation to be made effective It is evident that a single high blood sugar curve test may be without diagnostic value Whatever the explanation of a tendency toward lowering of successive curves, the fact that of our twenty-five subjects who had a high initial blood sugar curve, the second curve of twenty-one was lower, makes one loathe to conclude that a lowered

second curve ıs necessanly due to treatment or to expenmental procedure

CONCLUSIONS

1 Repeated blood sugar curves, some 300 ın number, have been made ın a group of 50 non-dıabetıc subjects, at ıntervals of days or months

2 In the majorıty of the subjects, there was progressıve lowenng of successıve curves followıng both ıngestıon and ınjectıon of glucose Of the 25 subjects wıth abnormally hıgh ınıtıal blood sugar curves, 21 of the curves were lower on second trıal A sıngle blood sugar curve test, therefore, may be wıthout dıagnostıc sıgnıficance, and a lowered subsequent curve may not necessarily be due to the expenmental or therapeutıc procedures ıntroduced between the first and second tests.

3 The unduly prolonged hyperglycemıa whıch follows ıngestıon of glucose and ınjectıon of adrenalın ın fastıng would seem to be due to the lack of stımulatıon of the sugar-regulatıng mechanısm

4 A mınorıty of the subjects studıed showed constant hıgh blood sugar curves and presumably belong to the group of persons from whıch dıabetıcs are to be recruıted.

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ABNORMAL SPECIFIC DYNAMIC ACTION OF PROTEIN, GLUCOSE, AND FAT ASSOCIATED WITH UNDERNUTRITION

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INTRODUCTION

Rubner (1) in 1902 developed the conception of a specific dynamic action for protein, glucose, and fat He thought that the extra heat produced during the digestion and oxidation of protein, glucose, or fat was derived from the intermediary metabolism of the foodstuffs themselves He also showed that this extra heat was waste heat, and that it could not be utilized by the organism for the production of muscular work

That this original conception of Rubner was in part incorrect has been shown by more recent studies Lusk and his associates have proved that, in the case of protein, the process of deamination and urea formation have no effect upon heat production (2) They have also presented experiments (3) showing no specific dynamic action in dogs with the amino acids, glutamic and aspartic, while glycocoll and alanin in a normal dog caused a marked increase in heat production Furthermore, Lusk (4) demonstrated that the specific dynamic action of glycocoll was independent of its oxidation Grafe (5) in 1915, in a series of experiments upon rabbits, dogs, and men, obtained evidence that glutamic acid, asparagin, phenylalanine, ammonium chloride and acetamid as well as glycocoll and alanin caused an increase in heat production More recently Atkinson and Lusk (6) presented a critical review of Grafe's work, and reported experiments with asparagin, aspartic and succinic acids, ammonium citrate and acetamid, finding in no case evidence of a specific dynamic action

In 1918 Burge and Neill (7) (8) reported that the increase in heat production associated with the eating of foods was accompanied by an increase of catalase in the blood, an enzyme which was able to liberate oxygen from hydrogen peroxide After a meat meal the increase in catalase was most marked They found that glycocoll and alanin produced an increase in catalase while glutamic acid did not Subsequently, Burge (9) conducted experiments to see if aspartic and succinic acids, acetamid and asparagin, would produce an increase in the blood catalase His conclusion was that the introduction of small amounts, 5 grams per kilo of body weight, of glutamic, aspartic, and succinic acids, asparagin, and acetamid produced no increase in catalase, while large amounts, 14 grams per kilo of body weight, did produce such increase This work has not been confirmed

More recently Aub, Everett and Fine (10) have reported observations upon the intravenous administration of glycocoll in urethanized and decerebrate cats Glycocoll given intravenously in 5 and 10 gram doses in four experiments showed no specific dynamic action in *urethanized* animals while in four experiments upon *decerebrate* cats with an average weight of 3 kilos, glycocoll given intravenously in 5-gram doses gave an average increase of heat production of 29 9 per cent

These facts tend to indicate that the specific dynamic action of protein, contrary to Rubner's original conception, is not inherent in the oxidation of the protein molecule itself Certain amino acids, while undergoing their own intermediary metabolism, apparently stimulate the tissue cells to produce more heat The observations of Grafe, contradictory to Lusk's experiments, were not subsequently confirmed by Lusk Since the report of Burge and Neill that the eating of foods was accompanied by an increase of blood catalase has not been confirmed, its significance cannot be evaluated The fact that Aub, Everett and Fine have reported the absence of specific dynamic action for glycocoll in urethanized animals may lead to observations that will throw light on the fundamental nature of the process

The mechanism of the extra heat production after the ingestion of glucose is thought to depend upon its combustion If the ingested

glucose is converted first into glycogen Johansson (11) reported that there was no extra heat produced Glucose, ingested by a diabetic and excreted in the urine, causes no increased heat production That absorption and circulation of glucose is without effect upon heat production was clearly shown by Lusk (12) in phloridzinized dogs Lusk ascribed the specific dynamic action of glucose as being due accordingly to an interrelationship between the circulating glucose and the metabolizing cells themselves, that is "the metabolism of carbohydrate plethora"

In the case of fat the fundamental mechanism of the extra heat production would appear to be of the same nature as that of glucose It depends directly upon the quantity of oxidizing fat, is parallel to the level of the blood fat, and likewise has been termed by Lusk, "the metabolism of fat plethora"

EXPERIMENTAL STUDIES

In this communication are reported six cases of disturbed nutrition, the onset and course of which in five was associated with definite subjective symptoms of ill health In these five cases there was a progressive loss of weight Studies upon the specific dynamic action of protein, glucose, and fat in all cases showed varying degrees of abnormality Regulation of the diet in accordance with the altered specific dynamic action resulted in a satisfactory gain in weight in four of the cases In the other two, sufficient time has not elapsed to make a definite statement When an improved level of nutrition had been established, in the three cases studied a marked change in specific dynamic action had taken place

In the determination of the specific dynamic action three types of meals were used a "protein" meal containing 150 or 200 grams of lean beef as stated, a "carbohydrate" meal of 100 grams of glucose dissolved in 300 cc. of lemonade which contained 60 cc. of lemon juice, and a "fat" meal composed of 200 cc of 20 per cent cream, 40 grams of butter, and 30 grams of toast.

The case reports of these six cases are appended

ANALYTICAL METHODS AND CALCULATIONS

Throughout the experimental periods all the cases were hospitalized Only in those cases where stated was a known intake of food maintained Between experiments there was no restriction of activity All basal metabolic rate determinations were conducted with the patient strictly controlled as to the "basal" state The prolonged respiratory experiments to determine the rise in heat production after the "protein," "glucose" and "fat" meals extended over three to six hours as stated A preliminary "basal" hour was observed in each experiment at the end of which the patient ate the meal With the subject remaining at rest in bed, expired air was collected in Douglas bags during the final ten minutes of the "basal" hour, and during the final ten minutes of each subsequent period The volume and temperature of the expired air was determined by a wet meter, gas analysis being completed in duplicate on the Henderson machine Fluid intake was maintained constant at 200 cc per hour Urine was collec ted each hour and total nitrogen determined by the Kjeldahl-Günning technique The non-protein respiratory quotients were calculated in the usual way The caloric value of oxygen for calculation of the non-protein calories was obtained from the tables of Zuntz and Schumberg as modified by Lusk (13) The protein calories were figured from the urinary nitrogen employing the factor 26 51 The calculation of the percentage increase of heat production above the "basal" level in the experimental periods was figured from the total calories produced

The meat given as the "protein" meal was analyzed for its nitrogen content each day, and its protein content obtained by using the factor 6 25 Since the 60 cc of lemon juice given with the "glucose" meal contained only three grams of carbohydrate as determined by analysis it was neglected in the calculations In the case of the "fat" meal the fat content of the cream was also determined For the calculation of the ingestion of protein calories the factor 4 1 and for the glucose calories the factor 3 74 were used

In those few observations where the basal metabolic rate was determined by oxygen consumption a Sanborn-Benedict closed system machine was used

The Sage Foundation standards of normal basal metabolism were employed throughout

THE NORMAL SPECIFIC DYNAMIC REACTION (AVERAGE)

Most studies upon specific dynamic action of the food factors have been conducted upon adult individuals or upon dogs Whether the increase of heat production after protein, glucose, and fat ingestion in the growing child is different from that of the adult is not known This point is of especial importance in this series of six cases as five of them varied from 14 to 18 years of age

Since the time of Rubner it has been known that the specific dynamic

action of protein was the greatest. He (1) calculated that the increased heat production for every 100 calories of protein ingested or metabolized was 30 9 calories for meat protein and in the case of a phloridzinized animal 31 9 calories for body protein Exact data obtained by indirect calorimetry has been reported by Carpenter and Benedict (14) on the normal individual after 200 and 150 grams of beef In two cases after 200 and 196 grams of beef containing 9 18 and 9 01 grams of nitrogen respectively the total increment increase of heat in three hours amounted to 25 and 28 calories In one case after 150 grams of beef containing 8 0 grams of nitrogen there were 24 calories of extra heat produced in three hours Aub and DuBois (15) have reported two experiments with 600 and 662 grams of beef, containing 23 7 and 24 1 grams of nitrogen respectively in which the extra heat produced from 1 5 to 5 5 hours after eating the meat amounted to 12 8 and 11 6 per cent of the energy value of the ingested protein calories Several other authors have published data after the ingestion of mixed meals which is very difficult to use for comparative purposes An outstanding point in such a survey is the marked variation in different individuals even with the same intake This is marked even in the standard work of Carpenter and Benedict

In the case of glucose Carpenter and Benedict (14) reported a total increment increase of heat of 18 calories in 4 hours after 100 grams plus one lemon This was the average of ten observations Gephart and DuBois (16) using 100 grams of glucose plus 10 cc of lemon juice reported an increase of 25 9 calories in 3 hours in one case, and an increase of 22 46 calories in 4 hours in another Thus glucose when given in 100 gram doses causes an extra production of heat to the extent of about 6 per cent of its energy value.

Studies upon pure fat by Magnus-Levy (17) indicated that the extra heat production amounted to about 2 5 per cent of the total calories ingested Carpenter and Benedict (14) reported that it was about 3 per cent of the fat calories ingested

For the purpose of controlling the reported observations like experiments were conducted upon five hospital patients who presented conditions unlikely to affect specific dynamic action This data is tabulated in tables 1, 2, and 3, and composite curves of the average percentage rise in heat production shown graphically in chart 1 In

TABLE 1

Specific dynamic action of protein (controls)

Hospital number	Date	Sex	Age	Percentage deviation from normal weight†	Test meal*: Lean beef	Test meal*: Protein	Test meal*: Protein calories	Basal metabolism rate	Calories per square meter per hour (basal)	Increase in heat production: 0 to 1 hour		Increase in heat production: 1 to 2 hours		Increase in heat production: 2 to 3 hours		Increase in heat production: 3 to 4 hours		Total heat increase, 4 hours	Percentage of ingested protein calories	Clinical diagnosis
	1926		*years*		*grams*	*grams*		*per cent*		*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	
44185	March 2	F	26	−26	200	43.4	178	−7.5	32.9	4.12	9.3	8.54	19.2	9.22	20.8	8.20	18.5	30.08	16.9	No disease
44687	May 5	M	41	−1	200	43.4	178	−15.9	31.8	4.43	8.1	7.08	13.0	9.13	16.7	10.28	18.8	30.92	17.4	Syphilis of central nervous system
45105	June 25	F	23	−23	200	49.2	202	+1.8	37.1	1.70	3.5	6.72	13.6	7.51	15.2	10.10	20.5	26.03	12.9	No disease
45145	July 7	M	22	+8	200	40.4	166	+3.5	40.4	14.62	21.8	10.10	15.0	9.32	13.9	7.72	11.5	41.76	25.2	Idiopathic epilepsy
	1927																			
46391	January 11	M	35	+18	200	37.8	155	−3.9	37.2	10.60	14.8	10.30	14.4	11.20	15.6	14.30	20.0	46.40	29.9	Myalgia
46058	January 14	M	19	−6	200	41.0	168	−14.5	34.6	2.60	4.9	6.61	12.5	9.96	18.8	10.71	20.2	29.88	17.8	Sub-acute rheumatic fever (convalescent)
46517	January 28	M	45	−5	200	39.2	161	−3.8	36.5	5.25	7.3	9.75	13.5	12.46	17.3	8.90	12.4	36.36	22.6	No disease
Average					200	42.0	173			6.19	10.0	8.44	14.5	9.83	16.9	10.03	17.4	34.49	20.4	

* Nitrogen content of beef determined in each instance.

† Standard weights taken from The Association of Life Insurance Directors and Actuarial Society of America, New York, 1912, pp 38 and 67

TABLE 2

Specific dynamic action of glucose (controls)

Hospital number	Date	Sex	Age	Percentage deviation from normal weight	Test meal (glucose)		Basal metabolism rate	Calories per square meter per hour (basal)	Increase in heat production								Total heat increase, 3 hours	Percentage of ingested glucose calories	Clinical diagnosis
									0 to 30 minutes		30 minutes to 1 hour		1 to 2 hours		2 to 3 hours				
	1926		*years*		*grams*	*calories*	*per cent*		*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	
45105	June 28	F	23	−22	100	374	−0.8	36.2	1.25	5.2	1.50	6.2	5.46	11.3	6.76	14.0	14.97	4.0	No disease
45145	July 12	M	22	+8	100	374	+4.4	40.5	3.50	10.4	3.90	11.6	6.50	9.7	5.58	8.3	19.48	5.2	Idiopathic epilepsy
	1927																		
46391	January 12	M	35	+18	100	374	−3.9	37.4	3.22	8.9	3.78	10.5	10.70	14.9	0.40	0.6	18.10	4.8	Myalgia
46058	January 17	M	19	−6	100	374	−13.2	34.9	2.13	8.0	2.25	8.4	3.75	7.0	3.23	6.1	11.36	3.0	Sub-acute rheumatic fever (convalescent)
46517	January 29	M	45	−5	100	374	−2.3	36.9	3.79	10.3	4.09	11.3	10.65	14.6	8.80	12.0	27.33	7.3	No disease
Average					100	374			2.78	8.6	3.10	9.6	7.41	11.5	4.95	8.2	18.25	4.9	

Glucose 100 grams in 300 cc. of lemonade (60 cc. lemon juice)

TABLE 3

Specific dynamic action of fat (controls)

Hospital number	Date	Sex	Age	Percentage deviation from normal weight	Test meal*						Basal metabolism rate	Calories per square meter per hour (basal)	Increase in heat production								Total heat increase, 4 hours	Percentage of ingested fat calories	Clinical diagnosis
					Fat		Carbohydrate		Protein				0 to 1 hour		1 to 2 hours		2 to 3 hours		3 to 4 hours				
	1926		*years*		*grams*	*calories*	*grams*	*calories*	*grams*	*calories*	*per cent*		*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	*calories*	*per cent*	
45105	June 29	F	23	−22	74	688	24	98	6	25	−2 0	35 6	4 11	8 7	5 69	12 0	7 70	16 3	8 26	17 5	25 76	3 7	No disease
45145	July 9	M	22	+8	71	688	24	98	6	25	+4 9	41 0	12 77	18 7	11 91	17 5	13 36	19 6	10 41	15 3	48 45	7 0	Idiopathic epilepsy
	1927																						
46391	January 13	M	35	+18	74	688	24	98	6	25	−1 9	38 4	6 35	8 6	7 92	10 7	8 32	11 2	4 70	6 3	27 29	4 0	Myalgia
46058	January 18	M	19	−6	74	688	24	98	6	25	−13 7	34 9	7 60	14 2	10 60	19 8	9 80	18 3	7 00	13 0	35 00	5 1	Sub acute rheumatic fever (convalescent)
46517	February 1	M	45	−5	74	688	24	98	6	25	−2 5	37 0	12 75	17 4	13 60	18 6	10 55	14 4	6 30	8 6	43 20	6 3	No disease
Average					74	688	24	98	6	25			8 71	13 5	9 94	15 7	9 94	15 9	7 33	12 1	35 94	5 2	

* Fat content of cream determined in each instance

the "protein" group, table 1, two additional cases have been included Unfortunately the age periods of these individuals does not correspond to that of the cases of undernutrition It will also be noted that their weights in three instances deviated considerably from the average for the given sex, age, and height In all except two cases, nos 44687

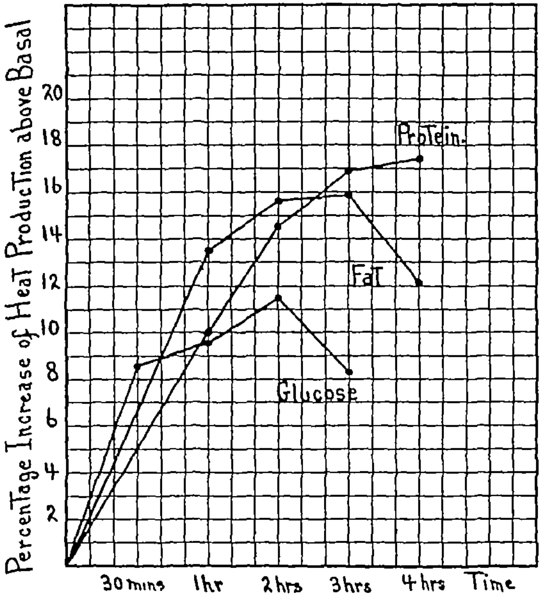

CHART 1 COMPOSITE CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL IN THE "CONTROL" CASES AFTER THE "PROTEIN," "GLUCOSE AND "FAT" MEALS

and 46058, the basal metabolic rates fell within the accepted normal variation of ±10 per cent In those two there was no determined reason why it should be a little below normal. In no case was it below minus 16 per cent In all these cases uniformity of basal heat production upon different days was obtained, well shown in the five

cases upon whom each of the three types of experiments were carried out This uniformity of the basal heat production lends accuracy to the experimental periods

The meals used were the same as in most of the experiments with the cases of undernutrition The "protein" meal contained 200 grams of lean beef, the "glucose" meal 100 grams of glucose plus 60 cc of lemon juice, and the "fat" meal 200 cc of 20 per cent cream, 40 grams of butter, and 30 grams of toast

In the case of the protein "controls" some individual irregularity was found in the time of the maximum percentage increase of heat production This was most marked in no 45145, who showed the greatest increment caloric increase in the first hour The average results of the seven experiments present a uniform percentage increase of heat production which reaches a plateau between the fourth and and the fifth hours The average total increment increase of heat production was 34 49 calories in 4 hours, individual variations ranging from 26 03 to 46 40 calories The average total increment increase of heat production in 4 hours was 20 4 per cent of the ingested protein calories

The individual variations in the five glucose "control" observations may be due to variations in the patients' glycogen reserves When these are depleted no rise in the respiratory quotient may follow the ingestion of glucose, as originally noted by Zuntz and Mering (18) This has been considered to be due to storage as glycogen, and Johansson (11) showed that if ingested glucose was first converted into glycogen no extra heat was produced The total caloric increment increase in 3 hours averaged 18 25 calories, which was 4 9 per cent of the total ingested energy intake

Since the rise in heat production after the ingestion of fat is supposed to be dependent upon oxidation, so the individual variations as seen in the fat "controls" may in part be explained The average percentage hourly increment increase presented a smooth curve The average total increment heat increase in 4 hours was 35 94 calories, being 5 2 per cent of the ingested fat calories Since the meal contained 98 carbohydrate calories, and 25 protein calories, the discrepancy between the usual accepted percentage caloric increase and the ingested fat calories, namely 3 per cent, can be partly explained

CASES REPORTED

State of nutrition of cases As will be seen from table 4, four of the six cases were females, and two males In all except one instance, case III, they had not attained adult development. Height was approximately normal for age except in case II where it was excessive Upon admission they were all markedly underweight for their age and height The degree of undernutrition varied from 21 to 40 per cent below the average for the given sex, age and height. The loss of weight prior to admission in the first five cases varied from 5 to 28 kilos Case VI had no history of a recent loss of weight, but he had been unable to maintain a normal level of nutrition since eight years

TABLE 4

Cases of undernutrition

Serial number	Sex	Age	Weight on admission	Height	Loss of weight	Percentage under weight	Average basal metabolism rate	Blood pressure	
								Systolic	Diastolic
		years	*kilos*	*cm.*	*kilos*	*per cent*	*per cent*	*mm. Hg*	*mm Hg*
I	F	14	27.5	146	18	33	−31	90	60
II	M	14	41.6	169	5	24	−15	98	64
III	F	31	34.1	158	23	40	−26	92	56
IV	F	18	43.8	162	18	21	−27	100	65
V	F	15	44.8	166	28	21	−15	110	60
VI	M	14	32.1	149	†	23	−4	112	70

* Standard weights taken from Association of Life Insurance Directors and Actuarial Society of America New York, 1912, pp 38 and 67

† No special loss of weight but failure to gain.

of age In the first five cases the basal metabolic rates were appreciably below normal, reaching the low figure in case I of minus 31 per cent With these low levels of basal metabolism the findings characteristic of myxedema were completely absent Blood pressures were not significant

Photographs of cases I, II, III, and VI taken upon admission are appended which give one a visual conception of the degree of undernutrition A second photograph of case I is also shown, taken in August, 1926, after nutrition had been re established

The uniformity of the basal metabolic rate in all cases and its parallelism in cases I and III to an improved state of nutrition is

TABLE 5

Cases of undernutrition—basal metabolism

Date	Weight	Surface area	R.Q	Calories per square meter per hour	Basal metabolism rate	Remarks
Serial I						
	kilos	*sq m*			*per cent*	
First Admission						
January 9, 1926	28 29	1 100		29 2	−32 1	O_2 consumption only
January 11	28 52	1 100		26 6	−38 1	O_2 consumption only
January 16	28 97	1 110	0 825	28 8	−33 0	Good coöperation
January 18	29 09	1 115	0 836	29 2	−32 1	Good coöperation
January 19	29 09	1 115	0 837	28 9	−32 6	Good cooperation
January 22	29 62	1 120	0 844	29 4	−31 6	Good coöperation
January 25	30 00	1 125	0 815	30 8	−28 2	Good coöperation
January 27	29 74	1 120	0 849	28 9	−32 7	Good coöperation
January 28	30 00	1 125	0 866	32 0	−25 7	Tired
February 1	30 45	1 130	0 815	31 1	−27 6	Tired
February 10	31 36	1 150	0 868	29 4	−31 6	Good coöperation
Average			0 837	29 5	−31 4	
Second admission						
August 11, 1926	40 45	1 290	0 782	35 0	−18 5	Good coöperation
August 12	40 45	1 290	0 788	35 3	−18 0	Good coöperation
August 13	40 45	1 290	0 780	35 2	−18 1	Good coöperation
Average			0 783	35 2	−18 2	
Third admission						
February 5, 1927	42 5	1 320	0 773	34 7	−19 3	Good coöperation
Serial II						
First admission						
March 22, 1926	41 59	1 445		38 6	−16 0	O_2 consumption only
March 23	40 90	1 435	0 779	40 2	−12 6	Good coöperation
March 24	41 59	1 445	0 780	38 5	−16 2	Good coöperation
March 25	41 36	1 440	0 800	40 4	−12 2	Good coöperation
Average			0 786	39 4	−14 2	
Second admission						
February 21, 1927	47 27	1 575	0 879	38 3	−16 6	Good coöperation
February 22	46 81	1 570	0 781	38 6	−16 0	Good coöperation
February 23	45 90	1 560	0 835	37 9	−17 7	Good coöperation
Average			0 831	38 3	−16 8	

TABLE 5—*Continued*

Date	Weight	Surface area	R.Q	Calories per square meter per hour	Basal metabolism rate	Remarks
			Serial III			
	kilos	*sq m*			*per cent*	
April 5 1926	34 09	1 260	0 882	27 2	−25 5	Good coöperation
April 8	34 09	1 260	0 783	27 7	−24 2	Good coöperation
April 13	34 09	1 260	0 745	26 6	−27 0	Good coöperation
April 28	35 73	1 280	0 730	28 0	−23 2	Good coöperation
May 3	35 73	1 280	0 728	25 9	−29 2	Good coöperation
Average			0 773	27 1	−25 8	
May 4, 1926	35 73	1 280	0 732	28 7	−21 3	Fair coöperation only
May 18	36 81	1 305	0 754	27 3	−25 3	Good coöperation
May 26	37 95	1 320	0 719	30 2	−17 3	Good coöperation
June 17	39 65	1 340	0 716	30 3	−16 9	Good coöperation
			Serial IV			
May 25, 1926	43 86	1 435		26 5	−30 3	O_2 consumption only
May 27	43 86	1 435	0 789	28 5	−25 1	Good coöperation
June 4	43 86	1 435	0 809	29 2	−23 2	Good coöperation
June 7	44 32	1 440	0 833	28 0	−26 3	Good coöperation
June 8.	43 52	1 430	0 818	27 4	−28 0	Good coöperation
Average			0 812	27 9	−26 6	
			Serial V			
December 17, 1926	44 77	1 470	0 799	36 8	−14 4	Good coöperation
December 21	45 00	1 472	0 917	36 4	−15 4	Good coöperation
December 22	44 32	1 465	0 797	36 3	−15 6	Good coöperation
Average			0 838	36 5	−15 1	
			Serial VI			
December 29, 1926	31 81	1 170	0 815	43 9	−4 5	Good coöperation
December 30	32 15	1 180	0 815	44 6	−3 0	Good coöperation
Average			0 815	44 3	−3 7	

TABLE 6

Specific dynamic action of protein, glucose, and fat in cases of undernutrition

Serial number	Experiment number	Date	Weight	Test meal: Protein		Test meal: Carbohydrate		Test meal: Fat		Calories per square meter per hour (basal)	Increase in heat production: 30 minutes		1 hour		2 hours		3 hours		4 hours		5 hours		Actual heat increase		Per cent of respective ingested calories		Remarks
		1926	*kilos*	*gm*	*cal*	*gm*	*cal*	*gm*	*cal*		*cal*	*per cent*	*cal*	*per cent*	*cal*	*per cent*	*cal*	*per cent*	*cal*	*per cent*	*cal*	*per cent*	*hrs*	*cal*	*meal*	*per cent*	
																											Before controlled diet
I	1	January 16	28 97	31 0	127					28 4			2 87	9 1	7 07	22 5	9 36	29 7					3	19 30	P	15 2	Protein 150 grams lean beef
	2	January 22	29 62	33 1	136					29 0			2 60	8 0	7 56	23 1	9 82	30 2	7 44	22 9	6 34	19 5	5	33 76	P	24 8	Protein 150 grams lean beef
	3	February 10	31 36			100	374			29 0	2 04	12 2	3 49	20 9	7 58	22 7	7 11	21 3					3	20 22	G	5 4	Glucose 100 grams
	4	January 27	29 74	6 0	25	24	98	67	623	28 4			5 92	18 7	9 75	30 7	7 07	22 3	7 76	24 5	9 11	28 7	5	39 61	F	6 3	Fat meal
	5	January 28	30 00							31 3	3 52	20 0	4 77	27 0	1 25	83 5	1 10	3 1					3	10 64	A		Adrenalin 0 5 mgm (Parke, Davis)
																											After controlled diet
	6	August 11	40 45	30 1	124					34 9			2 99	6 6	5 05	11 2	7 33	16 3	8 10	18 0			4	23 47	P	19 0	Protein 150 grams lean beef
	7	August 13	40 45			100	374			34 3	1 55	7 0	2 15	9 7	1 25	2 8	1 33	3 0					3	6 28	G	1 7	Glucose 100 grams
	8	August 12	40 45	6 0	25	24	98	74	688	35 0			3 80	8 4	0 99	2 2	5 20	11 5	2 37	5 2			4	12 36	F	1 8	Fat meal
		1927																									
	9	February 5	42 50	6 0	25	24	98	74	688	34 6			4 32	9 5	6 11	13 4	5 52	12 1	6 08	13 3			4	22 03	F	3 2	Fat meal
		1926																									
II	10	March 25	41 36	30 9	127					40 0			3 72	6 4	7 15	12 4	0 58	1 0	2 65	4 6			4	14 10	P	11 1	Protein 150 grams lean beef
	11	March 24	41 59			100	374			38 4			7 34	13 3	9 77	17 7	5 77	10 5					3	22 88	G	6 1	Glucose 100 grams
	12	March 23	40 90	6 0	25	24	98	66	586	39 7			9 93	17 4	11 49	20 1	10 34	18 2	6 79	11 9			4	38 55	F	6 5	Fat meal

		1927																								
	13	February 21	47 27	33 1	136					37 7			5 80	9 8	14 33	24 1	11 63	19 6	5 13	8 6			4	36 89	P	27 1	Protein 168 grams lean beef
	14	February 22	46 81			100	374			38 1	3 75	12 5	4 75	15 9	8 50	14 2	2 49	4 2					3	19 49	G	5 2	Glucose. 100 grams
	15	February 23	45 90	6 0	25	24	98	74	688	37 3			10 32	17 8	8 48	14 6	5 63	9 7	5 05	8 7			4	29 48	F	4 3	Fat meal
		1926																								
III	16	April 5	34 09	32 3	133					26 9			7 58	22 4	7 18	21 2	8 60	25 4	8 89	26 2			4	32 25	P	24 2	Protein 150 grams lean beef
	17	April 8	34 09			100	374			26 9			3 74	11 0	17 62	52 0	13 08	38 6					3	34 44	G	9 2	Glucose. 100 grams
	18	April 13	34 09	6 0	25	24	98	74	688	26 2			7 58	23 0	12 01	36 4	15 71	47 6	12 40	37 6			4	47 70	F	6 9	Fat meal
	19	May 3	35 73			100	374			24 7			3 96	12 5	6 26	19 8	8 88	28 1					3	19 10	G	5 1	Glucose 100 grams
	20	May 26	37 95			100	374			29 6	2 09	10 7	2 89	14 8	4 42	11 3	4 27	10 9					3	13 67	G	3 6	Glucose 100 grams
	21	June 17	39 65					60	558	29 8			1 06	2 7	1 78	4 5	4 69	11 7	4 22	10 6			4	11 75	F	2 1	Olive oil, 60 cc.
		1926																								
IV	22	June 7	44 32	40 0	164					27 6			5 72	14 4	6 35	16 0	4 90	12 4	4 63	11 7			4	21 60	P	13 2	Protein 200 grams lean beef
	23	May 27	43 86			100	374			28 1	0 11	0 5	1 61	8 0	2 35	5 8	2 11	5 2					3	6 18	G	1 6	Glucose. 100 grams
	24	June 4	43 86			100	374			28 6	0 35	1 7	1 20	5 9	2 12	5 2	2 38	5 8					3	6 05	G	1 6	Glucose. 100 grams
	25	June 8	43 52	6 0	25	24	98	74	688	26 9			4 27	11 2	7 20	18 8	9 97	26 0	10 14	26 5			4	31 58	F	4 6	Fat meal
		1926																								
V	26	December 21	45 00	38 6	158					35 9			3 37	6 4	4 27	8 1	7 12	13 5	7 1	13 6			4	21 93	P	13 9	Protein 200 grams lean beef
	27	December 17	44 77			100	374			36 3	1 61	6 1	2 37	8 9	4 80	9 0	3 86	7 2					3	12 64	G	3 4	Glucose 100 grams
	28	December 22	44 32	6 0	25	24	98	74	688	35 9			5 71	10 9	6 40	12 5	7 55	14 4	4 32	8 2			4	23 98	F	3 5	Fat meal
		1926																								
VI	29	December 30	32 13	38 2	157					43 8			8 03	15 5	8 20	15 8	12 07	23 3	1 19	2 3			4	29 49	P	18 8	Protein 200 grams lean beef
	30	December 29	31 81	6 0	25	24	98	74	638	42 9			6 35	12 7	13 18	26 2	10 77	21 3	9 20	18 3			4	39 50	F	5 7	Fat meal

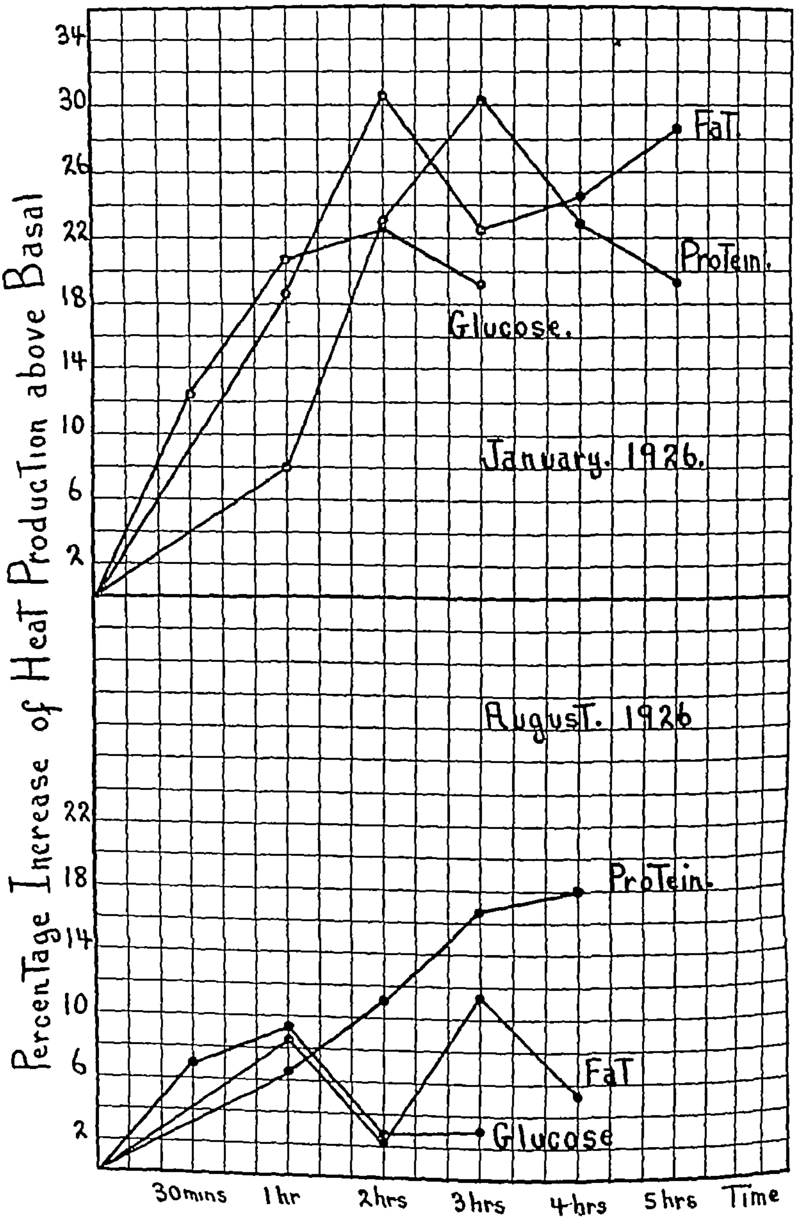

CHART 2 CASE I CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN," "GLUCOSE," AND "FAT" MEALS

In January, 1926, the weight was approximately 28 kilos, and in August, 1926, 40 45 kilos

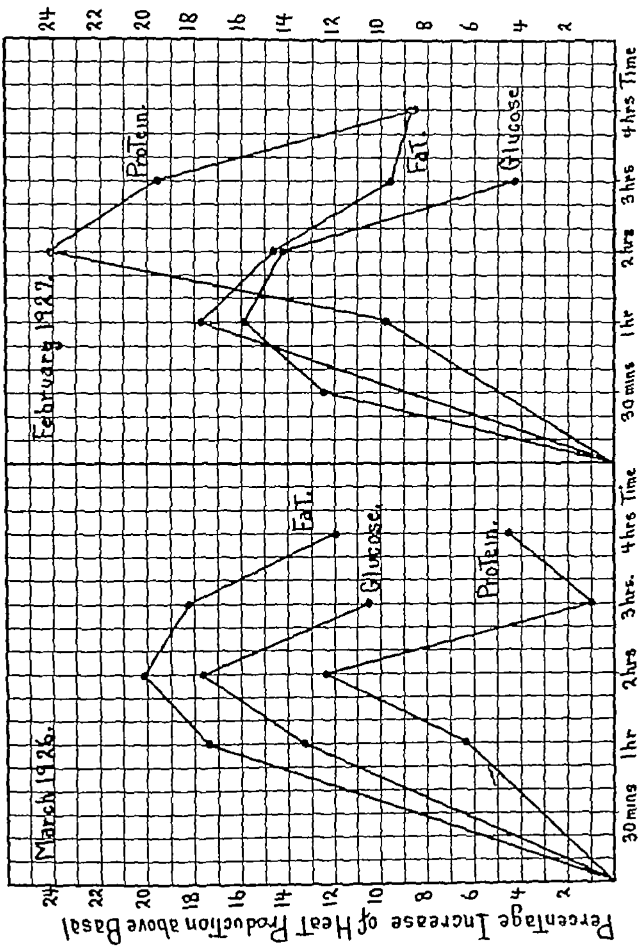

CHART 3 CASE II. CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN," "GLUCOSE," AND "FAT" MEALS

In March, 1926, the weight was 41 6 kilos, and in February, 1927, 47 kilos

shown in table 5 In case II there was no elevation of the basal metabolism associated with a gain in weight of approximately 5 kilos, possibly explained by the coincident increase in height

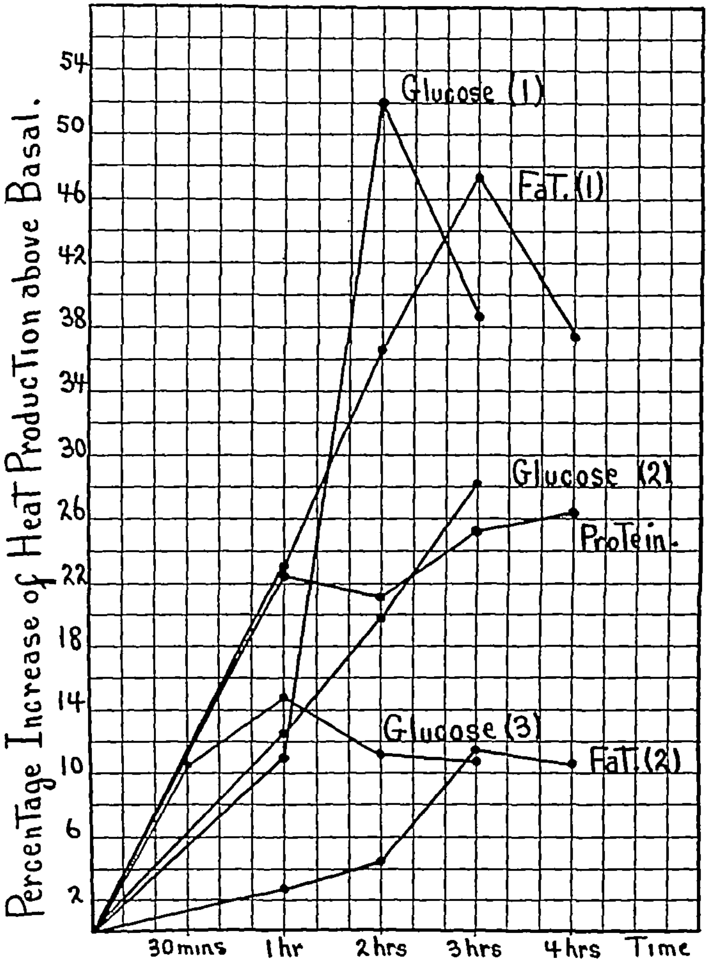

CHART 4 CASE III CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN," "GLUCOSE," AND "FAT" MEALS

All experiments were done during one admission see table 6 for details

Specific dynamic action of protein, glucose, and fat In each case the specific dynamic action of protein, glucose and fat was determined

The details of the experimental periods were as already stated, and the results are recorded in table 6 Graphs of the percentage increases of heat production are shown in charts 2 to 7 inclusive

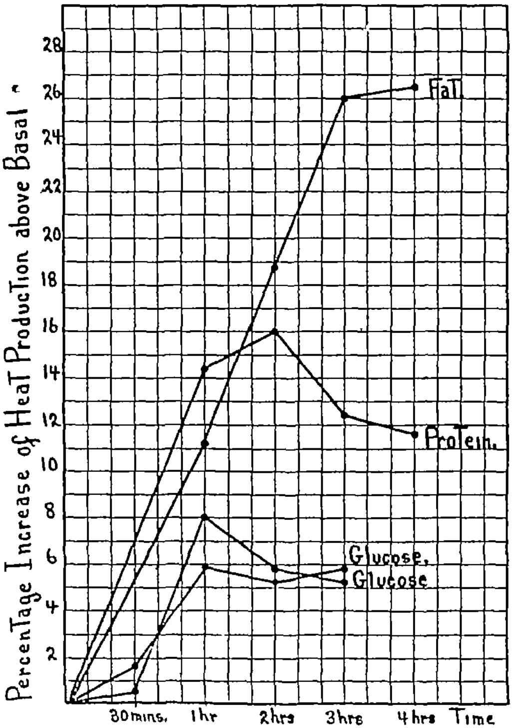

CHART 5 CASE IV CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN," ' GLUCOSE,' AND "FAT" MEALS

The two ' glucose ' experiments are duplicates

It will be noted that in the case of the "protein" meals only protein calories are recorded These were obtained by calculation from an

analysis of the nitrogen content of an aliquot sample of beef The carbohydrate in the 60 cc of lemon juice given with the glucose has been neglected The total calories of the "fat" meals are tabulated In the case of most of the "glucose" experiments expired air was collected at the end of 30 minutes and again at the end of 1 hour

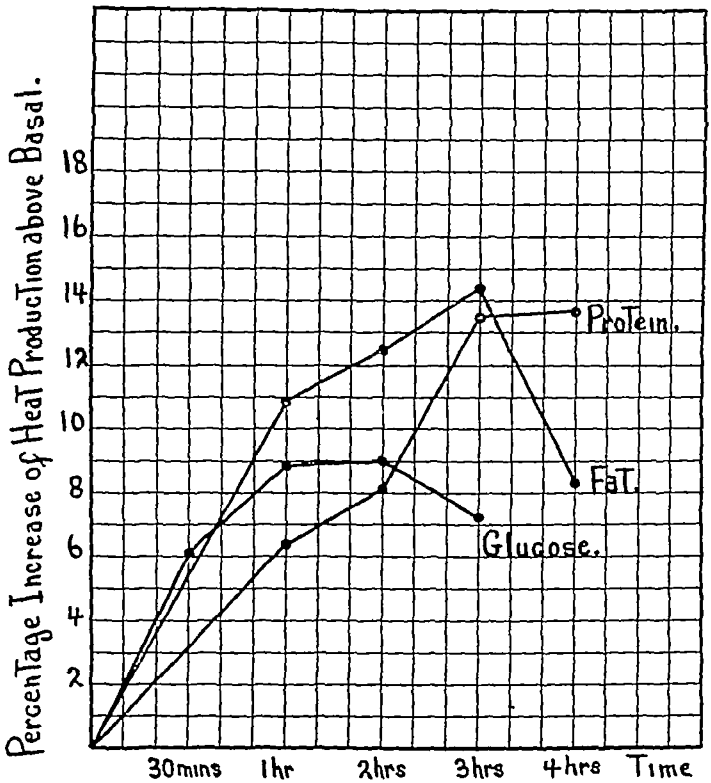

CHART 6 CASE V CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN," "GLUCOSE," AND "FAT" MEALS

Calculations of each were completed on an hourly basis and accordingly the percentage increase of the heat production is so recorded The actual caloric increase has been corrected for 30-minute periods This also applies to the adrenalin experiment, case I, no 5 Since the duration of the individual experiments was not sufficient in most instances for the elevated heat production to return to the

basal level, the actual heat increase as recorded only applies to the period of observation The relationship between the extra calories produced and the total calories ingested has been confined to the

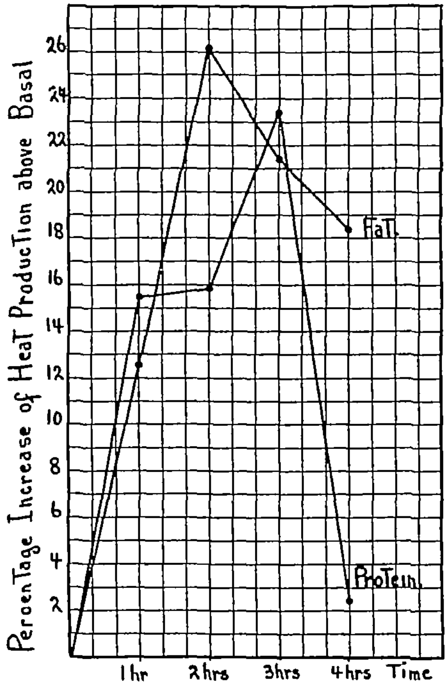

CHART 7 CASE VI CURVES OF THE PERCENTAGE INCREASE OF HEAT PRODUCTION ABOVE THE BASAL LEVEL AFTER THE "PROTEIN" AND "FAT" MEALS

protein, glucose, and fat calories respectively This was considered *to be wise so as not to confuse results and in view of the fact that the* "control" data was likewise calculated

In an analysis of this data consideration must be given to the uni-

formity of the basal level of heat production on different days as shown in comparable experiments

		Calories per square meter per hour
Case I	Experiments 1 to 4 inclusive	28 4 to 29 0
Case I	Experiments 6 to 8 inclusive	34 3 to 35 0
Case II	Experiments 10 to 12 inclusive	38 4 to 40 0
Case II	Experiments 13 to 15 inclusive	37 3 to 38 1
Case III	Experiments 16 to 18 inclusive	26 2 to 26 9
Case IV	Experiments 22 to 25 inclusive	26 9 to 28 6
Case V	Experiments 26 to 28 inclusive	35 9 to 36 3
Case VI	Experiments 29 to 30 inclusive	42 9 to 43 8

This constancy speaks for accuracy throughout the experimental periods

Specific dynamic action of protein The specific dynamic action of protein showed several marked variations from the "control" group In the composite curve of the latter (chart 1) there was a progressive percentage increase in heat production reaching its maximum in the fourth hour All the cases of undernutrition, except case V, showed a more rapid rise in heat production, in four, cases I, II, IV and VI, the maximum level being reached in the second or third hours This was promptly followed by a notable drop, quite unlike the normal reaction In cases II and V the percentage increase of heat production was below the normal throughout In case I at the time of undernutrition, experiments 1 and 2, the percentage caloric increase was greater than in the controls, while after a normal level of nutrition had been extablished an identical observation gave a low normal result, experiment 6 A subsequent observation was also obtained on case II With a weight of 41 36 kilos the percentage increase of heat production was definitely below the average normal result, experiment 10 Later, with a weight of 47 27 kilos, the maximum percentage increase of heat production was practically twice that previously obtained, experiment 13 In both experiments the maximum elevation was obtained in the second hour, followed by a rapid drop Of importance in the interpretation of experiments 10 and 13, case II, is the fact that coincident with a gain in weight from 41 36 to 47 27 kilos there was an increase in height of 7 9 cm

The actual extra calories produced in like periods of time averaged

considerably less in the cases of undernutrition than in the "control" group This is partly accounted for by the low basal level of the undernutrition cases and the fact that in four out of the six cases there was a premature sharp rise in heat production, to be followed by a rapid decline In case I, calculating experiments 2 and 6 on a four hour basis, 3 95 fewer calories were produced after good nutrition had been established Also, the relationship of the actual heat increase to the total ingested protein calories was slightly less in most instances than in the "control" group

The specific dynamic action of glucose In five of the cases experimental curves after like doses of glucose were obtained In cases I, II, and III the curves were repeated with an improved state of nutrition experiments 7, 14, 19 and 20 In four of the cases the maximum percentage increase of heat production was found at the end of the second hour as in the controls Cases I, II and III all showed a higher percentage level of heat production than the average of the controls throughout the experimental periods of three hours This was markedly so in cases I and III In the latter the percentage increase of heat production amounted to 52 0 and 38 6 per cent in the second and third hours respectively

In cases IV and V the percentage increase of heat production was much below the average in the controls That the state of nutrition of the individual was an important factor is indicated from the findings in cases I and III When the former weighed 31 36 kilos the percentage increase of heat production was much higher than in the controls, givng a total caloric increase in three hours of 20 22 calories experiment 3 The same case, weight 40 45 kilos, showed very little specific dynamic action for glucose, the total caloric increase in a like experiment being only 6 28 calories in three hours, experiment 7 In like manner case III, experiments 17, 19 and 20 showed a decreasing total heat increase in identical experiments, namely, 34 44, 19 10, and 13 67 calories with an improving state of nutrition

The percentage relationship between the ingested glucose calories and the total increment caloric increase was greater than in the average controls in cases I, II and III, and less in cases IV and V

Specific dynamic action of fat In five of the six cases the specific dynamic action of fat presented certain quite definite abnormalities

In all except case V the maximum percentage increase of heat production was much higher than in the average "control" group This was very noticeable in cases I, III, IV and VI, where the maximum was 30 7, 47 6, 26 5 and 26 2 per cent respectively These results are comparable to the maximum in the "control" group of 15 9 per cent In cases I, II and VI the rapidity of the rise of heat production was significant, the maximum percentage caloric increase being obtained in the second hour

TABLE 7

*Twenty-four-hour metabolism**

Case I

Time	R Q	Calories per hour	Calories above basal	Calories per square meter per hour	Percentage increase above basal	Remarks
1926						
January 25						
7 to 8 a m	0 815	34 26		30 5		Basal hour
8 05 a m						Breakfast
11 to 12 n	0 808	42 25	7 99	37 6	+23 2	
12 05 p m						Dinner
4 to 5 p m.	0 827	43 81	9 55	39 0	+27 8	
5 05 p m						Supper
8 to 9 p m	0 789	39 73	5 47	35 3	+15 7	
January 26						
7 to 8 a m.	0 810	35 02	0 76	31 1	+1 9	Basal hour
8 to 9 a m	0 856	34 92	0 66	31 0	+1 6	Basal hour

* Quiet in bed all the 25 hours

Diet Protein 56 grams, fat 118 grams, carbohydrate 150 grams

One-third of total diet for each meal.

The total caloric increase in comparable 4-hour periods averaged much the same in the cases of undernutrition as in the controls This was due to the lower basal level of the cases of undernutrition and the more rapid decrease in heat production after the maximum level had been attained The percentage increase of heat production in relationship to the ingested fat calories was greater in cases I, II, III and VI than in the average "control" group

In three cases, I, II and III, subsequent observations after an improvement in nutrition had taken place showed much less specific dynamic action for fat experiments 8, 9, 15 and 21

Effect of adrenalin in case I An observation after 0 5 mgm of adrenalin, experiment 5, gave a maximum percentage rise of heat production in thirty minutes of 20 0, in one hour of 27 0, falling practically to the basal level by the end of the second hour These findings are quite comparable with the observations of Boothby and Sandiford (19) on the calorigenic action of adrenalin

Twenty-four hour heat production in case I Observations on the total heat production were made throughout twenty four hours as shown in table 7 During this period the individual remained in bed, resting quietly most of the time Three meals were eaten as stated The basal level of heat production at the beginning and at the end of the period were almost identical. The maximum level of heat production was found four hours after dinner A calculation of the total heat production above the basal level throughout the twenty-four hours showed that the individual expended 124 6 calories, which was 6 41 per cent of the total caloric intake of 1942 calories, 13 per cent of the total calories produced, or 15 per cent of the basal level of heat production

DISCUSSION

The finding of abnormal specific dynamic action of the food factors associated with the development of marked states of undernutrition is considered to be of considerable significance That the abnormality may disappear when a more normal level of nutrition has been attained would be indicated by the later observations in cases I, II and III. That this increased specific dynamic action for certain foodstuffs is the factor that causes the loss of weight might be indicated by the gain in weight following restriction of that food factor in the diet. (See case histories for details of diets)

The fact that five of the cases ranged from 14 to 18 years of age is possibly of significance Whether at this period in life, when the development of secondary sexual characteristics is active, some endocrine unbalance develops one can only suggest That case II had certain findings characteristic of a future giant may be relevant Also the well-known finding of Plaut (20) and others that the Fröhlich's type of obesity shows very little specific dynamic action for protein is suggestive.

The low level of basal metabolism in the five cases where the undernutrition was associated with symptoms of ill health is considered to be due in part to the poor state of nutrition and in part to a compensatory mechanism that the body acquired to save heat under such circumstances. In cases I and III this was partly corrected with a gain in weight. In case II it remained unchanged but due to the gain in height associated with the gain in weight the general nutrition remained much the same.

The most marked abnormality seen in all cases except case V was the extraordinary rise in heat production after the "fat" meal. There was a much greater percentage rise than with the controls and the maximum level of heat production in three cases was attained at the end of the second hour. In two cases, cases I and III, this abnormality completely disappeared with an improved state of nutrition, and in case II it became appreciably less.

A comparison of the data of cases I, II and III, where subsequent like experiments were repeated after a gain in weight had taken place, failed to reveal any uniformity in the maximum level of heat production attained. That the state of nutrition can influence the specific dynamic action of protein was shown by McCann (21) in like experiments on a man at the end of a week's fast and after one week of normal diet. He observed that the maximum level of heat production was the same in the two observations.

SUMMARY

1. Six cases of undernutrition, five with and one without symptoms of ill health, are reported which show varying abnormalities of specific dynamic action for protein, glucose and fat. These abnormalities are compared with the findings in a "control" group of adult hospital patients.

2. The five cases in which the undernutrition was associated with symptoms presented basal metabolic rates varying from minus 15 to minus 31 per cent.

3. Regulation of food intake in accordance with the altered specific dynamic action resulted in a gain of weight in four cases. In the other two sufficient time has not elapsed to make a definite statement.

4 In cases I, II and III, coincident with a gain in weight, the abnormal findings with respect to specific dynamic action largely disappeared

CASE HISTORIES

Case no I Hospital no 43816

Present illness F N, a girl of 14 years was admitted to the Royal Victoria Hospital January 4, 1926 In her development there was nothing abnormal until July 1925, when she began to lose weight associated with a loss of appetite Due to unusual fatigue exercise was avoided In November, 1925, she noticed that her hands and feet were cold, and constipation became troublesome

A physician advised a high fat diet but upon eating such meals she noticed that her skin became warm and flushed for a period of about three hours Loss of weight became progressively more marked, decreasing from 45 45 kilos in July, 1925, to 27 5 kilos upon admission

Personal history Birth was normal, the delivery being spontaneous During infancy she was rather small but fat, and was breast fed for twelve months Throughout childhood she developed normally, being plump with "bright red cheeks" until the onset of the present trouble in July, 1925 She had measles and chicken pox as a child and menstruation began at twelve years of age It was rather irregular for the first year and during the last three months has been absent. Mentally she was very bright, leading her class at school

Physical examination Height 146 cm, weight 27 5 kilos, temperature, 97°F, pulse, 76 The general appearance was that of a pale-skinned young girl who looked about two years older than her stated age Her face and trunk were thin, the bony landmarks being prominent There was little subcutaneous fat and the skin was of a dry texture There was no edema. Both the lateral lobes and the isthmus of the thyroid gland were slightly enlarged, but of a soft uniform consistency There was no evidence of increased vascularity All the subcutaneous lymphatic glands were small, palpable, but not tender The heart and lungs were normal Blood pressure was systolic 90 and diastolic 60 mm Hg The abdomen was negative Both knee jerks were absent.

Special examinations The urine showed no abnormalities The red blood cells were 4,100 000 per cubic millimeter, whites 5,200 per cubic millimeter, and the hemoglobin was 75 per cent The vital capacity was 100 per cent according to West's standards The blood Wassermann was negative X ray examinations of the chest, skull, stomach, and duodenum showed no abnormalities The fasting blood sugar was 0 08 per cent, rising after the ingestion of 100 grams of glucose in 30 minutes to 0 14, in 60 minutes to 0.20, and in 180 minutes to 0 18 per cent respectively The basal metabolic rate remained relatively constant averaging minus 31 4 per cent (table 5)

Summary The above physical and special examinations showed only an

emaciated young girl with a dry skin and a slightly enlarged thyroid gland, low blood pressure, and absent knee jerks The "glucose curve" showed possible evidence of delayed glycogen storage and the basal metabolic rate was markedly lowered (See photograph taken January, 1926)

Subsequent course of case On the basis of the finding of a marked abnormality of the specific dynamic action for fat a diet rather low in that factor was given The values were protein 75 grams, fat 75 grams, and carbohydrate 250 grams, making 2030 calories At the institution of this diet her weight was approximately 30 kilos From then on there was a progressive gain, in February, 1926, 32 kilos, in April, 1926, 35 kilos, and in August, 1926, 40 5 kilos In August, 1926, she was re-admitted for investigation

Re-admission Hospital no 45395 The general state of nutrition was excellent (see photograph taken in August, 1926) The skin was not dry, the thyroid gland was just palpable, the blood pressure was systolic 115, and diastolic 78 mm Hg , and the knee jerks were active Amenorrhea was still present Rectal examination showed an infantile uterus The basal metabolic rate averaged minus 18 2 per cent (table 5) A marked change in the patient's specific dynamic action for fat, glucose and protein had taken place (table 6 and chart 2)

Subsequently, in February, 1927, weight was found to be 42 5 kilos, the basal metabolic rate minus 19 3 per cent, and the specific dynamic action for fat definitely less than the average normal (table 6 and chart 2) There had been no change in height

Since August 1926, an average normal diet has been eaten

Case no II Hospital no 44374

Present illness M S , a boy of 14 years was admitted to the Royal Victoria Hospital March 18, 1926 He was quite well up until two years previously when he began to grow rapidly With the rapid growth he became weak, lost his appetite, and began to lose weight The latter had amounted to 5 45 kilos at the time of admission The personal and family histories were unimportant

Physical examination Height 169 cm , weight 41 6 kilos, temperature 98°F , pulse 80 Patient was a tall thin boy, both thighs showing horizontal striae due to stretching of the skin The development of the secondary sexual characteristics was well marked The heart and lungs were normal, with a blood pressure of systolic 98 and diastolic 64 mm Hg The basal metabolic rate averaged minus 14 2 per cent (table 5) An x-ray of the skull showed the sella turcica to be larger than normal, but there was no evidence of any erosion of the bone Further special examinations disclosed no abnormalities The state of nutrition is well shown in the photograph taken upon admission

Subsequent course of case On the basis of the abnormal specific dynamic action for fat, a diet containing approximately 75 grams of protein, 75 grams of fat, and 250 grams of carbohydrate was given By February, 1927, the weight had increased to 47 2 kilos and the height to 176 9 cm

Re-admission Hospital no 46747 On February 20, 1927, he was re-admitted The basal metabolic rate was minus 16 8 per cent The specific dynamic action experiments were repeated Due to the gain in height of 7 9 cm., the general state of nutrition was about the same

Case no III Hospital no 44313

Present illness A O, a married woman of 31 years of age was admitted to the Royal Victoria Hospital March 12, 1926 She was quite well up until October, 1925, when she had an attack of jaundice associated with fever After four weeks in bed the jaundice disappeared, but she remained weak, had no appetite, and began to lose weight. Food caused a sense of discomfort in her epigastrium Weakness became very marked, confining her to bed for three months prior to admission. The loss of weight was approximately 23 kilos

Personal history Menstruation was regular up until October, 1925, but since then it had been absent

Physical examination Height 158 cm, weight 34 1 kilos, temperature 98°F, pulse 100 The picture was that of an extremely emaciated young woman, suffering from marked mental depression A thorough examination including gastro intestinal, gall bladder, and liver function studies failed to account for her present state There was slight epigastric tenderness and very slight motor delay in the stomach The blood pressure was systolic 92 and diastolic 56 mm, Hg The basal metabolic rate averaged minus 25 8 per cent. The photograph shows her state of nutrition

Progress of case In view of the abnormal rise in heat production after glucose and fat, a diet of protein 100 grams, fat 100 grams, and carbohydrate 150 grams was given At first it was a continual struggle to get her to eat food, but with persistence a slight gain in weight commenced By discharge on June 21, 1926 her weight had increased to 40 kilos and she had few complaints With the gain in weight her mental attitude improved and she was up and about the ward each day On June 17, 1926, the basal metabolic rate was minus 17 per cent Coincident with the gain in weight and the rising basal metabolism there was a great decrease in the abnormal rise in heat production after glucose and fat

Case no IV Hospital no 44879

Present illness V H., admitted to the Royal Victoria Hospital May 19, 1926, was a young woman of 18 years Two years previously, when weighing 61.36 kilos, amenorrhea started Shortly coldness of the hands and feet was noticed and constipation developed Her skin became dry, weakness developed and loss of weight was progressive After eating, a dragging sensation developed in the epigastrium By May, 1926, the loss of weight had amounted to 18 kilos

Physical examination Height 162 cm, weight 43 8 kilos, temperature 98°F, pulse 68 The appearance was that of a greatly emaciated young woman The skin was dry but not thickened and the feet and hands were cold The heart and

lungs were normal The blood pressure was systolic 100 and diastolic 65 mm Hg Further studies showed moderate visceroptosis and the basal metabolic rate averaged minus 26 6 per cent

Progress of case In accordance with the altered specific dynamic action findings a diet was given which contained 80 grams of protein, 75 grams of fat, and 240 grams of carbohydrate For several months there was no gain in weight, but gradually she began to gain and in February, 1927 weighted 56 4 kilos With the gain in weight all symptoms except moderate constipation disappeared Menstruation recommenced in October, 1926

Case no V Hospital no 46257

Present illness E T, a girl of 15 years, was admitted to the Royal Victoria Hospital December 13, 1926 At the age of 12 years she weighted 72 72 kilos and menstruation commenced Gradually she began to lose weight until December, 1925, her weight was 59 54 kilos Shortly she became unusually tired, taking little exercise, and appetite became poor In March, 1926, her weight was 62 27 kilos, in June, 1926, 59 54 kilos, in September, 1926, 54 54 kilos, and in October, 1926, 50 45 kilos Upon admission it was 44 8 kilos

Physical examination Height 166 cm, weight 44 8 kilos, temperature 97°F, pulse 70 The appearance was that of an undernourished, pasty girl The heart and lungs were negative and the blood pressure was systolic 110 and diastolic 60 mm Hg The urine showed a trace of albumin when in the upright position which disappeared when lying down A careful study of the renal function gave normal results The basal metabolic rate averaged minus 15 1 per cent

Progress of case Due to the finding of an abnormal elevation of heat production after a "fat" meal she was given a diet containing only 1 5 grams of fat per kilo body weight, its total caloric content being equal to her theoretically normal basal metabolism plus 75 per cent The values were protein 90 grams, fat 75 grams, and carbohydrate 390 grams Her symptomatic improvement has not been very satisfactory The weight has increased to 47 7 kilos (February 16, 1927) No further observations have been obtained

Case no VI Hospital no 46328

Present illness B R, a boy of 14 years, was admitted to the Royal Victoria Hospital, December 26, 1926 He had no symptomatic complaints but due to his state of undernutrition he was admitted for investigation

Personal history Patient was a full term baby and breast-fed for a few weeks only Throughout infancy his nutrition was satisfactry He had the usual children's diseases Since about the age of eight has been thin and of a high strung temperament He takes part in all games and stands well in school

Physical examination Height 149 cm, weight 32 1 kilos Although only a boy of 14 years the appearance was that of an older individual The whole body was lean but well proportioned The cheeks were hollow and wrinkled The secondary sexual characteristics were not well developed No organic abnormali-

ties could be detected The blood pressure was systolic 112 and diastolic 70 mm Hg The basal metabolic rate was minus 3 7 per cent A photograph is appended

Progress of the case With the finding of a markedly increased specific dynamic action for fat, a diet was planned which contained 3 grams of protein and 2 grams of fat per kilo body weight, and enough calories to be equivalent to the theoretical basal plus 75 per cent The values were protein 96 grams, fat 64 grams, and carbohydrate 350 grams A verbal communication to date, February, 1927, stated that no gain in weight had taken place

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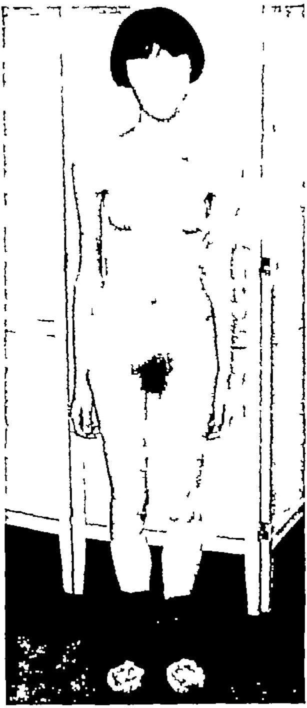

Fig 1 Fig 2

Fig 1 Case I January 1926 Weight 27 5 Kilos
Fig 2 Case I August, 1926 Weight 40 45 Kilos

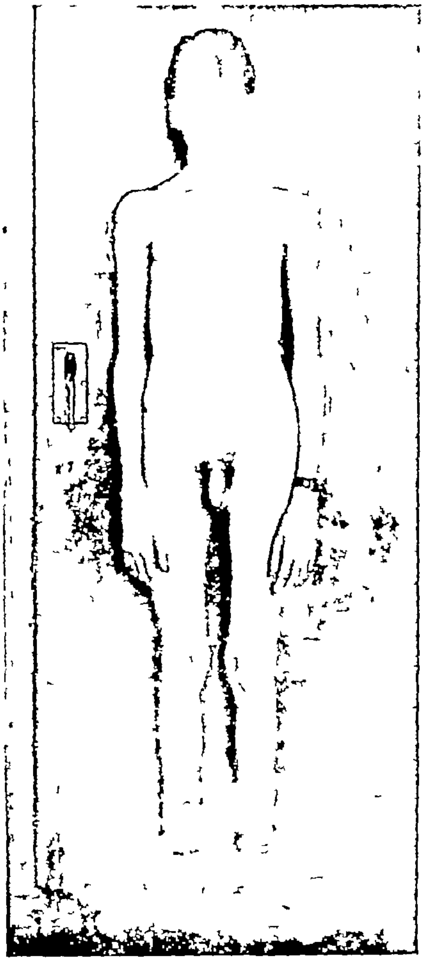

Fig 3

Fig 4

Fig 3 Case II March, 1926 Weight 41 6 Kilos
Fig 4 Case III April 1926 Weight 34 1 Kilos

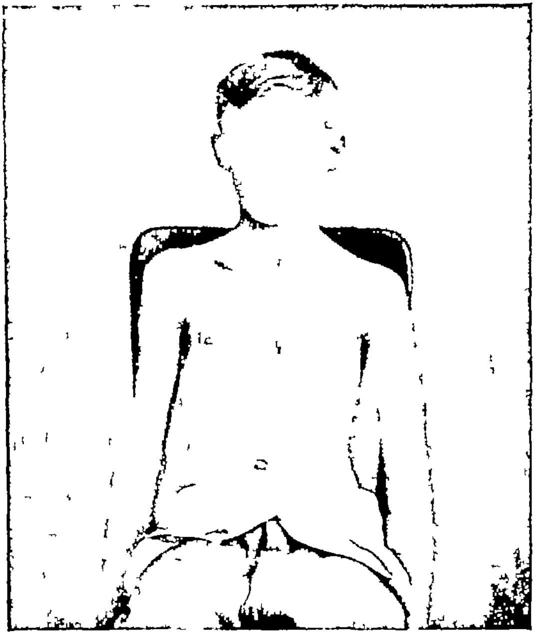

FIG 5 CASE VI DECEMBER, 1926 WEIGHT 32 1 KILOS

STUDIES ON THE VELOCITY OF BLOOD FLOW

VI The Method of Collecting the Active Deposit of Radium and Its Preparation for Intravenous Injection[1]

By HERRMANN L. BLUMGART and SOMA WEISS

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(Received for publication April 13, 1927)

In establishing a satisfactory method for measuring the velocity of blood flow by means of the intravenous injections of radium C, the collection of the active deposit of radium from radium emanation (radon) and the preparation of the active deposit for intravenous injection became problems of the utmost importance.

A THE METHOD OF COLLECTING THE ACTIVE DEPOSIT OF RADIUM

The problem Radium emanation is, of course, a gas A consideration of the problem involved showed that a satisfactory means of collecting the active deposit of radium from radium emanation would have to fulfill the following requirements (*a*) The method must provide some means of combining the contents of a number of tubes each containing a relatively small amount of radium emanation The reason for this is a practical one. The tubes containing 20 or more millicuries of radium emanation are valuable for therapeutic purposes, whereas tubes containing 5 or 10 millicuries are more limited in their usefulness and can therefore be dispensed with at times In order to utilize these tubes of emanation it was therefore essential to devise some means whereby, for example, five tubes containing 10 millicuries each could be crushed and the resulting 50 millicuries utilized in one unit as a source of active deposit of radium (*b*) The process of crushing the tubes and the transfer of the liberated emanation to a proper receptacle must be accomplished without the possi-

[1] This investigation was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases

bility of loss of any radium emanation The escape of even a minute amount might result in the diffusion of the gas about the laboratory Since the method of measuring the velocity of blood flow depends upon a detecting device of great sensitivity, liberated emanation might disturb the entire experimental procedure A loss of radium emanation would, moreover, not be economical (*c*) The chamber for holding the emanation must be absolutely air tight but must nevertheless permit the introduction and withdrawal of the electrode used for collecting the active deposit without allowing any of the emanation to escape (*d*) The amount of active deposit collected must be a reasonably high percentage of that theoretically possible Unless this requirement were fulfilled, the amount of radium emanation necessary would be unduly large (*e*) The procedure must use the same radium emanation for repeated collections of active deposit without the loss of any emanation save through the natural rate of its decay (*f*) The active deposit of radium must be collected without any possible contamination by radium emanation or by any other substance which might be deleterious if injected intravenously (*g*) The entire procedure must be simple and dependable

The procedure adopted Initial attempts were made to collect the active deposit upon sodium chloride which was exposed to the radium emanation in a high vacuum The procedure was found to be uncertain and time-consuming It therefore seemed that a simpler method which did not necessitate high vacua might prove more reliable

Rutherford (1) showed in 1900 that when an emanating compound of thorium is placed in a positively charged, closed vessel, the active deposit could be concentrated on a negatively charged wire H W Schmidt (2), and Wellisch and Bronson (3), in 1908 and 1912 respectively, demonstrated that, similarly, the active deposit of radium could be concentrated on the negative electrode if the emanation were exposed to strong electric fields These investigators showed that, in a field of about 200 volts, between 80 and 90 per cent of the active deposit could be concentrated on the insulated, axially situated negative electrode The conditions of their experiments hardly conformed to the requirements of the collection of the active deposit for intravenous injection Though these investigators did not state

the actual quantity of active deposit collected, they were presumably dealing with relatively small amounts of radium emanation where high yields would be more easily attainable

After considerable experimentation we have found the design of

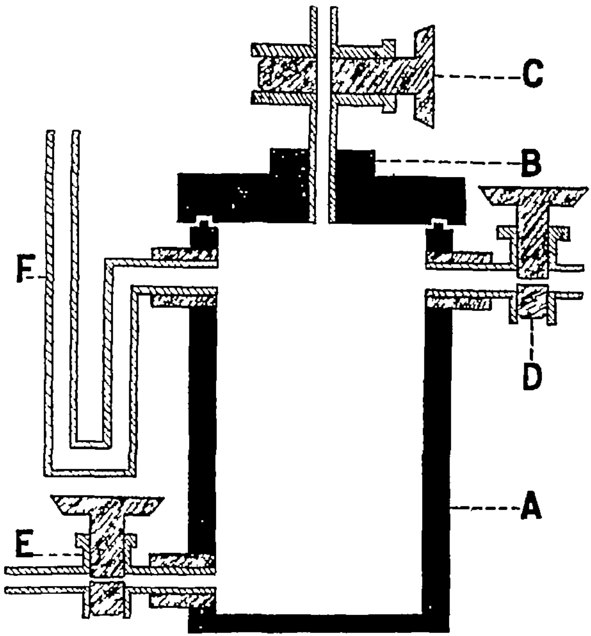


FIG 1 DIAGRAM OF EMANATION CHAMBER USED FOR THE COLLECTION OF THE ACTIVE DEPOSIT OF RADIUM

the chamber figured below to be adequate for the preparation of the active deposit of radium The steel chamber (fig 1) which contains the radium emanation consists of the cylinder A, to which is fitted a hard rubber top plate B The steel chamber A is 9 cm high and 5 cm in diameter Stopcock C whose bore is centrally situated in

respect to the cylinder allows one to introduce the platinum electrode upon which the active deposit is to be collected Stopcock E permits the introduction into or escape of mercury from the chamber A glass manometer tube is inserted at F in order that one can observe at all times the relation of the pressure within the chamber to the pressure existing in the room The radium emanation is introduced into the chamber through stopcock D All stopcocks are accurately fitted to the chamber and then sealed by means of DeKhotinsky cement The rubber top is sealed to the steel chamber by means of heavy stopcock grease

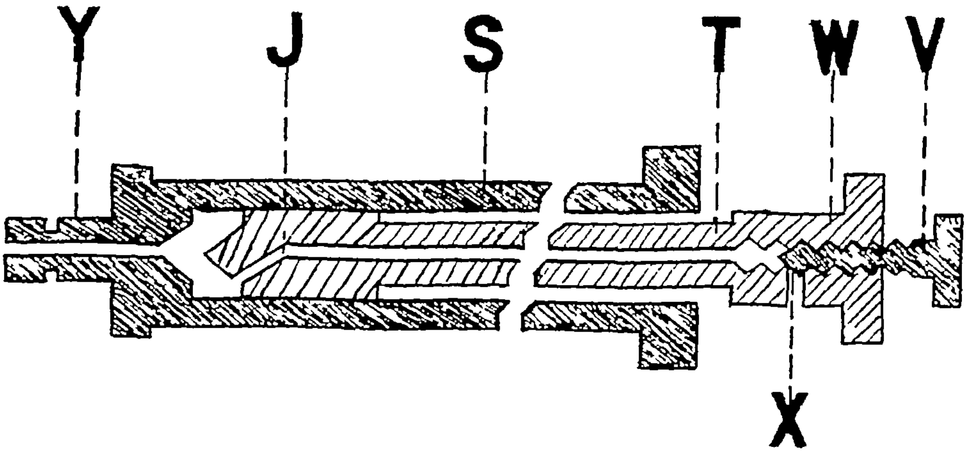


FIG 2 DIAGRAM OF DEVICE USED FOR CRUSHING GLASS TUBES CONTAINING RADIUM EMANATION AND INTRODUCING LIBERATED EMANATION INTO CHAMBER

The radium emanation tubes are crushed by means of the breaking device shown in figure 2 S is the barrel of an ordinary 5 cc "Record Syringe" The handle usually attached to the plunger was removed and in its stead a hollow tube was soldered to the piston J The bore of the hollow brass tube T communicates at one end through a small hole drilled in the piston with the interior of the barrel of the syringe, and at the other end through a needle valve arrangement V X W with the room air

The actual procedure is as follows The walls of the steel emanation chamber are carefully cleaned and mercury is introduced into the

chamber so that the level of the mercury is 5 cm below the top of the chamber The manometer F is filled with mercury and the top rubber plate B is sealed on Stopcock D is closed and negative pressure is established in the chamber by aspirating air through stopcock C The chamber is tested for several hours to be certain that it is air tight

The breaking device is then attached to stopcock D of the emanation chamber by means of a short rubber connection Next the small glass tubes containing the radium emanation are placed at the bottom of the syringe and the plunger is inserted into the barrel By keeping the needle valve freely open the tip of the plunger can be

TABLE 1

Determination number	Duration activation	Millicuries of radon in source	Millicuries on electrode	Percentage of the theoretical obtainable
	minutes	*millicuries*	*millicuries*	*per cent*
1	60	39	10 7	54
2	65	34	12 2	64
3	90	26	11 2	58
4	180	25	13 4	54
5	240	17	8 9	52
6	60	53	16 5	60
7	50	53	11 9	54
8	50	53	14 7	67
9	110	45	18 8	48
10	50	51	14 6	67

brought down close to the emanation tubes The needle valve is then screwed shut A small piece of rubber tubing is attached to the manometer F and clamped with a hemostat Stopcock C is then connected to a source of high vacuum and the chamber is exhausted with all other stopcocks closed Stopcock C is then closed, and stopcock D is slowly opened The tubes in the syringe are then crushed by the plunger J By opening the needle valve V (fig 2) to the room air at X and at the same time rotating the plunger TW, the liberated radium emanation is washed into the chamber which is now at negative pressure The radium emanation being now delivered to chamber A, stopcock D is closed The emanation being now safe in the chamber A, room pressure is again established either

by allowing mercury to draw through stopcock *E* or by allowing air to enter through *C* until the manometer pressure reading is zero To arrange for this new (room) pressure is important, for the opening *C*, through which the platinum needle is now to be introduced, could not be sealed in order to retain the emanation by a few drops of mercury unless inside and outside pressures were equal A centi-

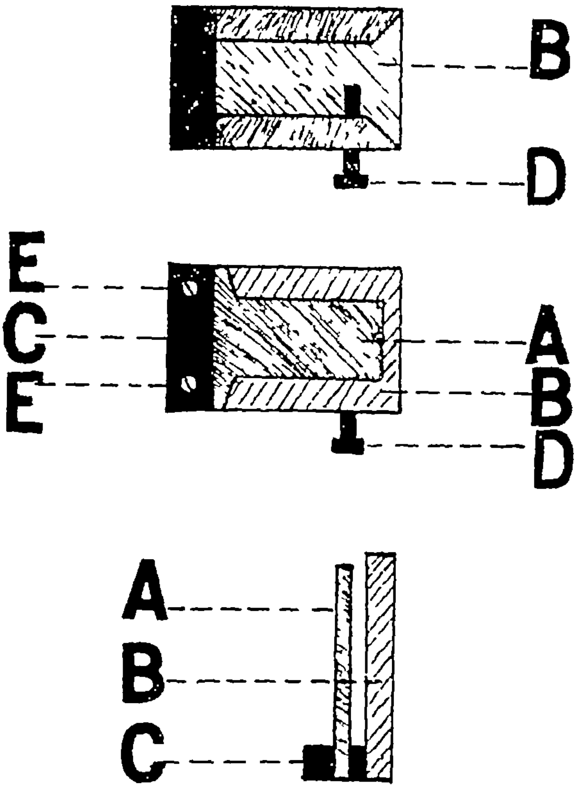
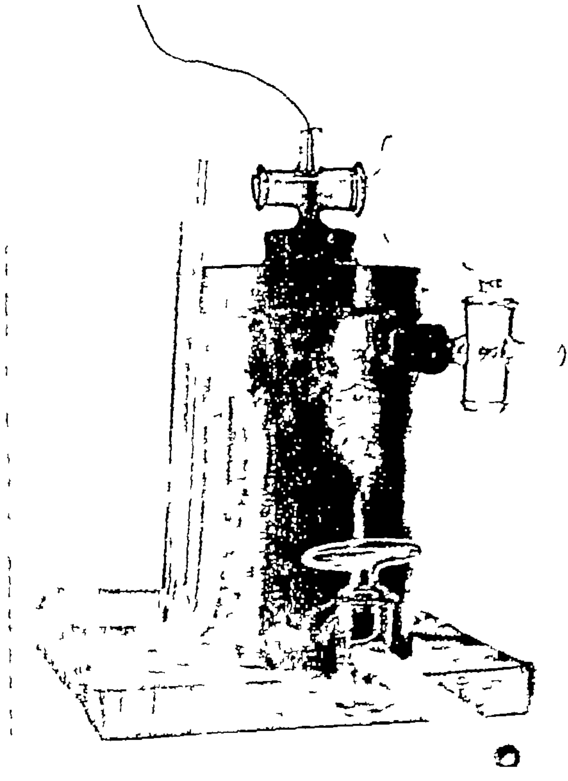


Fig 3 Diagram of Clip for Automatically Recording Time of Injection

meter length of rubber tubing is accordingly attached to stopcock *C* and filled with a few drops of mercury A length of No 20 platinum wire on which, as has been said active deposit is to be collected is inserted through stopcock *C* into the chamber It is important that the point of the platinum needle be 2 5 cm above the level of the mercury The tip of the wire should be sharp The wire is



The results obtained by the procedure are given in table 1 Higher yields could probably be obtained by further experimentation but such attempts have not been made since the present method satisfies our practical needs

When, through natural decay, the amount of radium emanation becomes inconveniently small, additional amounts of radium emanation may be added to the chamber without discarding the amount still present With stopcocks *C* and *D* closed, mercury is allowed to drain from the chamber through stopcock *E* until considerable negative pressure has developed as noted by reading manometer *F* Stopcock *D* is then opened, the new tubes are crushed according to the procedure previously outlined, the needle valve is opened, and the radium emanation washed into the chamber

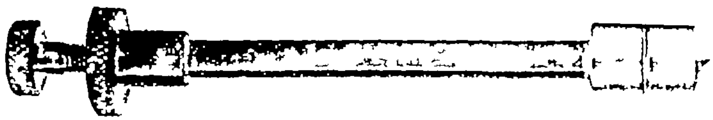


FIG 5 DEVICE USED FOR CRUSHING EMANATION TUBES AND INTRODUCING THE RADIUM EMANATION INTO CHAMBER

B THE METHOD OF PREPARATION OF THE ACTIVE DEPOSIT AND ITS INTRAVENOUS INJECTION

The platinum needle is removed from C and inserted into a small glass tube which has previously been half filled with 10 per cent hydrochloric acid The active deposit is thereby dissolved The needle is removed and the active deposit hydrochloric acid solution is neutralized to phenol red by means of NaOH The volume of the resultant solution is not more than 0 1 cc The dissolved active deposit NaCl solution is drawn up into a tuberculin syringe and is then ready for use The syringe is attached to a three-way stopcock to one opening of which a needle is attached for intravenous injection The other connection communicates with a manometer containing

citrate solution, by means of which the venous pressure is measured according to the method of Moritz and Tabora (4)

To the handle of the plunger of the syringe is attached a small clip (fig 3) *B* is a brass shoulder which fits over the flange of the syringe handle and is firmly secured by the screw *D* *A* is a thin leaf of copper which is inserted into the hard rubber *C* and insulated by it from *B* When the intravenous injection is accomplished by pressure on the leaf *A*, an electrical circuit is closed through *A* and *B* and the time and duration of the intravenous injection are automatically recorded on the moving tape of a siphon feed galvanometer recorder

We wish to thank Dr William Duane for his interest and advice

CONCLUSIONS

1 The details of a method for collecting the active deposit of radium from radium emanation and its preparation for intravenous injection are described

2 Because of the simplicity of the procedure and the relatively high yield of active deposit attainable, the method is well suited to the purposes of the determination of the velocity of blood flow in man

3 When, through the natural period of decay, the amount of radium emanation becomes inconveniently small, additional amounts of radium emanation can be added to the chamber without discarding the amount in previous use

4 The details of a method for breaking several tubes each containing a small amount of radium emanation, and the process of transferring the liberated gas to an ionization chamber without loss of any of the emanation is described

5 A device for automatic registration of the time and duration of intravenous injection is described

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STUDIES ON THE VELOCITY OF BLOOD FLOW

VII The Pulmonary Circulation Time in Normal Resting Individuals[1]

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(Received for publication May 2, 1927)

This paper presents the first measurements of the velocity of blood flow through the lungs of man Thorough understanding of the blood flow through the lungs is of great significance in understanding adaptations of the circulation in health and disease

The study of the pulmonary circulation has, therefore, always attracted the interest of investigators The literature is voluminous and was reviewed in 1903 by Tigerstedt (1) and in 1921 by Wiggers (2)

In animals the study of the pulmonary circulation necessitates such distortion of the normal physiological conditions that interpretation of the results is difficult. The chest has usually been opened, the negative intrathoracic pressure abolished, and normal inspiration has been replaced by forcible distention of the lungs with positive blasts of air By such methods Plumier (3) in 1904 first studied the pulmonary circulation time in animals, estimating the time between release of a previously compressed vena cava and the subsequent maximal rise in arterial pressure G N Stewart (4) (19) advanced the knowledge of the pulmonary blood flow by studying the time required for dyes and salt solutions to pass from the great veins through the heart and lungs to the great arteries The chest was not opened although the animals were under general anesthesia His results will be discussed later

Because such experiments are clinically not feasible, and because

[1] This investigation was aided by a grant from the De Lamar Research Fund and from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases

the results of investigations on animals can be translated into terms of human physiology only with difficulty, the study of the pulmonary circulation in man has been pursued along somewhat different paths The most trustworthy information has been elicited by studying the pulmonary minute volume flow by the principle of Fick Although exceedingly important information has been obtained, the usefulness of the procedure has been limited because of certain inherent difficulties The analysis of air and blood samples is complicated, and collection of air samples demands intelligent cooperation on the part of the subject The clinical usefulness of the procedure has also been restricted because the method is inapplicable in the presence of profound circulatory disturbance associated with dyspnea To quote recent investigators, "the existing methods applicable to human subjects require intelligent cooperation and they are at best tedious and subject to error" (5) In short, the existing methods for studying the pulmonary minute volume flow are inadequate and no method for measuring the velocity of blood flow through the lungs in man is available

Previous studies (6, 7, 8, 9, 10, 11) have shown that the arm to arm circulation time can be measured in man by injecting the active deposit of radium into the antecubital vein of one arm and subsequently, by means of a suitable detecting device, noting its time of arrival in the arteries about the elbow of the other arm It seemed that if the procedure for measuring the arm to arm circulation time could be adapted to the measurement of the pulmonary circulation time in man, the information obtained would be valuable for the following reasons 1 Information would be secured about a fundamental aspect of the pulmonary circulation hitherto unstudied in man 2 The pulmonary circulation could be studied under both normal and pathological conditions without in any way interfering with the phenomena under observation 3 The method would be quantitative, objective, and require no cooperation from the patient 4 The effect of the variability of the peripheral capillary circulation would be obviated Previous investigators as, for example, G N Stewart (12), and Hewlett and Van Zuwaluenburg (13) found considerable variations in the volume flow of the arm which bore no constant relation to general bodily conditions

Since the circulation of blood through the lungs has considerable physiological and clinical significance, it seemed desirable to measure the velocity of blood flow through the lungs complicated as little as possible by extraneous factors Small changes might be of considerable significance and still be entirely obscured by relatively large fluctuations in the arm blood flow After considerable experimentation, the following procedure has been found most satisfactory in the the study of the velocity of blood flow through the lungs

METHOD

The principle of the method The method is a further development of the procedure devised for the study of the arm to arm circulation time The active deposit of radium, that is to say, radium C, is injected into the antecubital vein of one arm and its time of arrival is observed first, in the right chambers of the heart, and later in the arteries about the elbow of the other arm As mentioned in previous studies, active deposit of radium is particularly suited to the purpose Of primary importance is its non-toxicity in amounts used Quick and Duffy (14) at the Memorial Hospital in New York, in studying the possible therapeutic effects of radium C in patients with advanced generalized carcinomatosis, repeatedly gave intravenous injections of 50 and 75 millicuries, amounts five to eight times those used by us, without any consequent ill effects They studied the urine for signs of renal irritation and the blood for evidence of nitrogen retention without noting any untoward reactions No significant changes occurred in the red cell count or hemoglobin

The injection of radium C by us into animals, and later into ourselves and other normal subjects has shown a uniform absence of any objective or subjective ill effects over a period of time in which four hundred and fifty measurements of the velocity of blood flow have been made In a few instances, short temporary thrombosis of the injected vein occurred without causing any ill effects to the patients The incidence of thrombosis in our experience was no higher than that occurring with other diagnostic procedures In the first one hundred and fifty patients the urine was examined before and after the obser vation, and in no instance were any signs of the slightest renal irrita tion disconcernible, nor were any changes in the blood noted None

of the patients has shown any delayed reaction This is of particular interest in connection with ourselves, for not only have we measured our blood flow by injecting active deposit of radium, but we have been exposed to the beta and gamma radiation of the active deposit used in all the observations Hence, through such cumulative effects, any untoward reaction would become manifest earlier in us than in patients

The absence of any demonstrable biological effects of radium C in the course of our investigations is in no way surprising for the amounts necessary for a measurement of the velocity of blood flow is but 1 to 10 millicuries of active deposit of radium Such an amount is infinitesimal and corresponds in weight to 10^{-15} grams It should

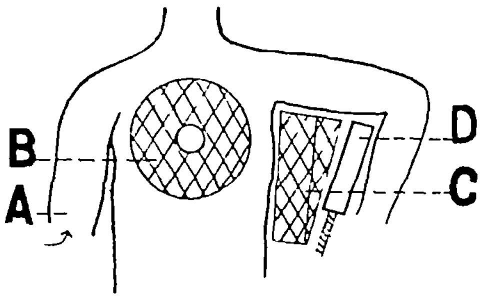

FIG 1 RELATION OF PATIENT TO DETECTORS AND LEAD SHIELDS

be noted that millicuries of active deposit do not correspond in weight to radium itself for a millicurie of active deposit signifies the amount which is *in equilibrium* with a millicurie of radium emanation A millicurie of emanation, in turn, is that amount which is *in equilibrium* with a milligram of radium element

The character of the radiation of active deposit is peculiarly suited to velocity of blood flow measurements Of the three types of radiation emitted by radioactive substances, the so-called "alpha radiation" is most likely to cause possible toxic effects Within twenty minutes after the active deposit has been removed from the emanation, the alpha radiation decays to 4 per cent of its initial value The rapid spontaneous decay of active deposit to a practically inert form, radium D, prevents prolonged exposure of a person to the radiation Active deposit decreases to 3 per cent of its initial activity within

three hours Less than the theoretical 3 per cent is present in the body at the end of three hours, however, for a considerable portion of the injected amount is excreted into the intestines and into the urine Consequently, repetition of the test after three hours is feasible

In the studies of the velocity of blood flow, active deposit of radium has been used because of its penetrating radiation, which consists of beta particles (or electrons), and gamma rays which are comparable to hard x rays These radiations can penetrate ordinary material such as tissues or air, but are absorbed by lead If, therefore (see fig 1), the active deposit of radium is injected into the vein of one arm at *A*, the active deposit gives off radiations as it is carried up the arm to the right chambers of the heart But the lead shield *B* prevents the radiation from reaching the detecting device which has been inserted within the centrally situated hole This hole is placed immediately over the right auricle (over the sternum in the third intercostal space) so that, upon the arrival of the active deposit within that chamber, the radiations are no longer separated from the detector by lead Instead, the radiations emerge through the tissues, traverse the air, enter the detecting device and there set up a train of events, finally producing automatic registration of the time of arrival of the active deposit within the right chamber of the heart

Similarly the radiation from the active deposit as it is carried through the lungs is prevented from reaching the detector *D* by the intervening lead shield *C* Once the active deposit reaches the arterial vessels immediately in front of the detector *D*, the radiations set up a chain of events similar to that already described by which their time of arrival is automatically registered The time that elapses between the injection of the active deposit into the antecubital vein at *A*, and the arrival of the active deposit in the right chambers of the heart may be called "the venous velocity time" for it is a measure of the velocity of the venous blood of the arm to the heart The time that elapses between the arrival of the active deposit of radium in the right chambers of the heart and its arrival in the arteries about the elbow of the arm may be called the "crude pulmonary circulation time" The latter includes besides the actual pulmonary circulation time, the time spent in passing through the four cardiac chambers and the time necessary for the active deposit to travel through the large arterial trunks

to the place of detection in the antecubital arteries For reasons which will subsequently be given, the time spent in the heart is approximately one second and the time necessary for the active deposit to travel from the heart to the antecubital arteries is approximately three and three-tenths seconds Consequently if four and three-tenths seconds are subtracted from "the crude pulmonary circulation time" one obtains an estimate of "the actual pulmonary circulation time"

Originally it was hoped that by placing a detecting device immediately above the heart, as indicated in figure 1, the arrival of the active deposit could be ascertained, and that with the passage of the active deposit into the vessels of the lungs, the ionization effect would diminish only to increase when the active deposit of radium was concentrated again within the left chambers of the heart Unfortunately, once the ionization effect is observed in the detector placed over the heart, the effect remains persistently present Further efforts will be made, however, to measure the time of appearance and diappearance of the active deposit in the left chambers of the heart

Description of the apparatus The results of the present investigation are based on the detection of the time of arrival of the active deposit in the right chambers of the heart of man and in the arteries about the elbow of the left arm Instead of the modified C T R Wilson cloud chambers used in the previous "arm to arm circulation time" studies, a smaller detecting device has been utilized This detecting device which was built and generously loaned to us for our particular purpose by the General Electric Company of Schenectady, New York, is described elsewhere by C W Hewlett (15) (fig 2) In principle this device depends upon the fact that radiations of radium C cause ionization by collision in any gas subjected to high potential differences *M* (fig 2) represents a small brass cylinder with a thin aluminum leaf window *A* at one end *N* is a plug of hard rubber which holds the axially situated platinum electrode *L* in position *M* is charged to 1200–2000 volts, depending upon the point of the platinum electrode In the absence of any radioactive substance the air gap serves to insulate the platinum needle at −4 5 volts from the walls of the brass chamber at 1500 volts A single electron or gamma ray may produce sufficient ionization by collision to cause a slight diminution in the voltage on the needle This fall of potential is converted

into current flow by a three electrode vacuum tube In the plate circuit of this tube is a recording pen galvanometer manufactured by Mr A A Clokey of Rutherford, New Jersey Attached to the moving coil Y (fig 2) of the galvanometer CXY (fig 2) is a light glass capillary which records any movements of the galvanometer on a moving paper

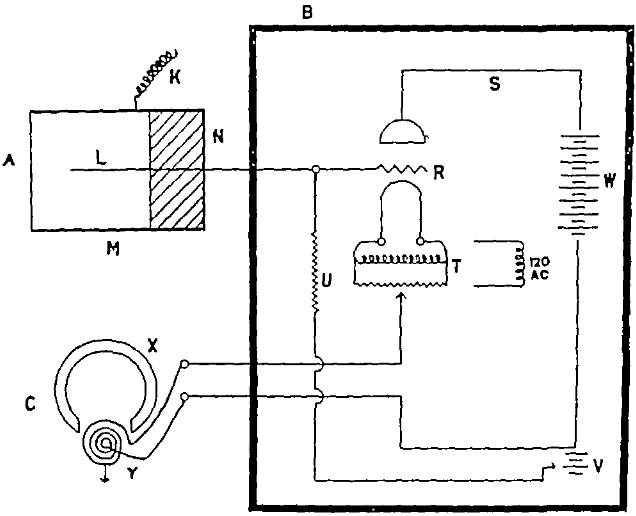

FIG 2 DIAGRAM OF DETECTOR AND RECORDING SYSTEM

M indicates brass cylinder, A thin aluminum window K, lead for high voltage, N, hard rubber plug, L, platinum needle, B amplifying unit consisting of R, three electrode vacuum tube T, transformer for filament of tube, S, plate of tube, W, plate batteries, V batteries for bias for high grid resistance U, and XYC recording pen galvanometer

tape The appearance of radium C beneath the detector instantly produces a train of events which terminates in the automatic inscription by a pen and ink record on a moving paper tape By means of a signal magnet and time clock the time is also recorded in seconds

The lead shields B, and C (fig 1) are designed to absorb the

maximal percentage of radiation Shield *B* is 22 cm in diameter and 17 cm in height The diameter of the centrally bored hole is 4 cm The ionization chamber is placed within the block with its window or lower end 10 cm from the bottom of the block The lead block *C* consists of several separate parts designed to utilize the available space between the arm and the thorax The position of the lead block can be adjusted by means of a hydraulic pump device, which was built and generously loaned to us by the General Electric Company, Schenectady, New York

Critique of method To observe whether the active deposit of radium produces ionization in the detector before it arrives in the right chambers of the heart would theoretically demand continuous withdrawal of blood from the right auricle and of making tests for the presence of radium C simultaneously with the inscription of the record Obviously this is not feasible Instead, with the apparatus arranged precisely as in the actual velocity tests, active deposit of radium equivalent or greater than the amount usually injected was brought gradually toward the hole in the lead block along a path similar to that traveled within the veins leading to the right chambers of the heart Many observations have uniformly demonstrated the fact that the appearance of the active deposit beneath the hole is signalled immediately by a continuous ionization effect of such increased magnitude as to leave no doubt as to the precise position of the source of the radiation

The same considerations discussed in a previous paper (7) regarding the critique of the method apply to the measurement of the time of arrival of the active deposit in the antecubital arteries of the arm and will not be repeated The method of detection is exactly similar except that a small ionization chamber is used instead of the more cumbersome modified C T R Wilson cloud chamber The sensitivity of both detectors is identical and results obtained by one device are in complete accord with those gained by means of the other

Procedure of the measurement of the pulmonary circulation time The preparation of the active deposit and the technique of its intravenous administration is described in a previous communication Measurement of the velocity of blood flow is made under basal metabolic conditions, no food being taken by the patient after supper of the

preceding evening The person lies at rest in bed at least twenty minutes before the test The site of arterial pulsation of the brachial artery is marked with ink and the left arm is passed around the lead blocks so that the window of the detector is just in front of the line of maximum arterial pulsation The position of the right auricle is indicated by a circle of ink painted on the skin of the chest over the sternum between the third and fourth ribs The patient is placed with the spot of ink immediately beneath the hole in the lead block (fig 1), *B* The ionization chamber with its cable leading to the amplifier and recording systems is then inserted into the hole of the lead shield The active deposit, the volume of which does not exceed 0 2 cc , is not injected for at least twenty minutes after it has been removed from the

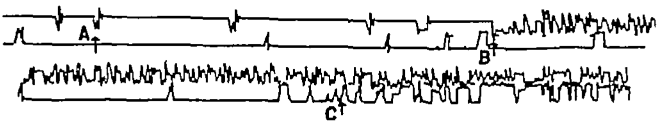

Fig 3 Record of Pulmonary Circulation Time Measurement

Middle dots signify time in seconds Upper line is the tracing made by the recording pen of the detector over the right auricle, lower line, similar record of the detector placed against the brachial artery *A* indicates the instant of injection into right antecubital vein, *B*, the time of arrival of active deposit into right auricle, *C*, the time of arrival of active deposit in the left antecubital arteries

radium emanation in order to allow a decrease of alpha ray activity to 4 per cent. The precautions previously described are observed in carrying out the intravenous injection (7, 11)

As the active deposit is carried in the blood stream to the right chambers of the heart, an occasional deflection of the galvanometer recorder of the heart detector can be seen With the arrival of the active deposit in the right chambers of the heart, the emergent beta particles and gamma rays pass through the tissues of the chest, traverse the air, and entering through the thin window of the ionization chamber, set up a continuous disturbance in a siphon feed recording pen of the galvanometer which registers in ink on a moving tape. The occasional deflections occurring before the continuous activity of the galvanometer are due to the occasional gamma rays which penetrate

the lead block Elimination of these occasional deflections would require a lead block of undue proportions The arrival of the radium active deposit in front of the detecting device is accompanied by an ionization change of such magnitude as to leave no doubt of its time of arrival (fig 3) The time between the intravenous injection and the arrival of the substance in the right heart represents the velocity of blood flow between the two points As the active deposit travels through the body, an occasional disturbance occurs in the detector placed against the artery of the arm With the arrival of the active deposit within the arterial vessels about the elbow, emergent beta particles and gamma rays pass into the ionization chamber and produce a continuous disturbance which is registered on the same tape by a second siphon feed recording pen galvanometer The time is marked in seconds by an electromagnetic timer The time of injection may be automatically recorded by the device described in a previous communication (11) Consequently the paper tape serves for the automatic registration of all the data

All the persons in whom the velocity of pulmonary blood flow was measured were either healthy or convalescent from some disease which was neither cardio-respiratory, metabolic, or haemic in nature Many of the patients were from the surgical services and were ready to be discharged from the hospital Physical examination revealed no cardio-respiratory abnormalities The temperature, the pulse and the respiration were noted The pulse was again counted immediately upon the completion of the observation The age was recorded and the weight, height and arterial blood pressure measured The venous pressure was estimated by the direct method of Moritz and Tabora (16), just before the active deposit of radium was injected The vital capacity was taken immediately on the completion of the measurement of the velocity of blood flow The results of our observations are tabulated below (table 1)

Figure 4 graphically presents the incidence of the variations in the velocity of the venous blood from the arm to the heart and figure 5 in similar manner presents the data in regard to the crude pulmonary circulation time Comparison of these two diagrams indicates that the fluctuations in the pulmonary circulation times are less than that of the venous velocity time

TABLE 1

Duplicate measurements of the pulmonary circulation time in the same person

Number of measurements	Date	Name	Age	Surface area	Pulse rate	Vital capacity	Vital capacity per square meter	Arterial pressure		Venous pressure H_2O	Circulation time			Circulation time per square meter		
								Systolic	Diastolic		Arm to heart	Arm to arm	Pulmonary	Arm to heart	Arm to arm	Pulmonary
				square meter		*cc.*	*cc*	*mm.*	*mm.*	*cm*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*
275	October 26 1926	C. W	17	1 60	105	3,700	2,312	126	64	+3 0	5 5	12 5	7 0	3 4	7 8	4 3
310	November 19, 1926	C W	17	1 60	93	4,300	2 690	114	54	−1 0	5 5	13 0	7 5	3 4	8 1	4 7
311	November 19 1926	M. A.	23	1 67	77	Patient unable to coöperate		124	58	+16 0	11 5	20 0	8 5	6 9	11 9	5 0
314	November 23, 1926	M A	23	1 67	85			124	76	+11 0	5 5	16 5	11 0	3 3	9 8	6 5
373	February 18 1927	J S	23	1 74	83	4,400	2,525	126	72	+8 0	9 0	19 0	10 0	5 1	10 9	5 2
374	February 18, 1927	J S	23	1 74	96	4 400	2 525	126	72	+6 5	11 5	18 0	6 5	6 6	10 3	3 7
375	February 23, 1927	J M	21	1 84	69	4,900	2,662	110	76	−1 5	7 0	21 5	14 5	3 8	11 6	7 8
378	February 23, 1927	J M	21	1 84	66	4,900	2 662	110	76	−1 0	8 0	19 0	11 0	4 3	10 3	5 9
382	February 26, 1927	P M	21	1 57	67	4,100	2,611	126	64	−1 0	4 5	15 5	11 0	2 8	9 8	7 0
383	February 26, 1927	P M.	21	1 57	76	4,100	2,611	126	64	−0 5	6 5	18 5	12 0	4 1	11 7	7 6
390	March 16, 1927	A. W	22	1 66	60	4,200	2,529	106	68	+18 0	14 0	26 0	12 0	8 4	15 6	7 2
392	March 16 1927	A W	22	1 66	63	4,200	2,529	106	68	+6 5	6 5	20 5	14 0	3 9	12 3	8 4
400	March 21, 1927	H. B	36	1 51	78	2 900	1 921	112	60	−2 0	7 0	20 0	13 0	4 6	13 2	8 6
402	March 21, 1927	H. B	36	1 51	80	2,900	1,921	112	60	−1 5	6 0	21 0	15 0	3 9	13 9	9 9
286	October 28, 1926	G Y	24	1 74	98	Unable to obtain		174	84	+13 0	3 5	10 0	6 5	2 0	5 7	3 7
413	April 21, 1927	G Y	24	1 74	98			128	76	+11 5	7 0	13 5	6 5	4 0	7 7	3 7

* To conform to the level of the right auricle, 5 0 cm should be added to these figures

In order to learn what variations may occur in a given individual repeated measurements were performed under conditions as similar as possible The results are presented in table 1 The maximum variation was three and a half seconds and the average in eight persons was two seconds Table 2 presents our findings in sixty-two tests The data include measurements of the pulmonary circulation time, the venous velocity time, the vital capacity, and the arterial and

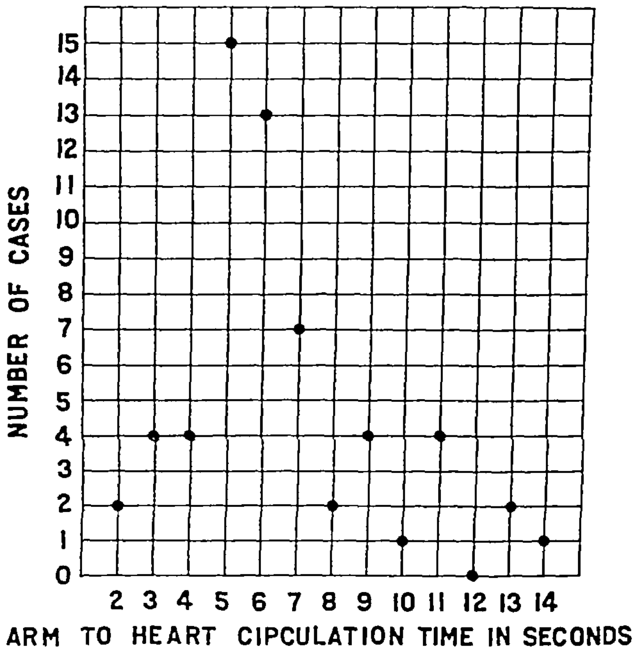

FIG 4 THE VELOCITY OF VENOUS BLOOD FROM THE ARM TO THE HEART—IN 62 CASES

venous pressures The venous velocity time varied from two to fourteen seconds The average venous velocity time in fifty-nine measurements was seven (6 7) seconds, the pulmonary velocity time varied from five to seventeen, the average crude pulmonary circulation time (sixty-two measurements) was eleven (10 8) seconds

In certain individuals, the pulmonary circulation time was longer than seventeen seconds This was accompanied at times by a prolongation in the venous velocity time and was not infrequently asso-

ciated with an unduly high venous pressure Some of these persons had definite stigmata of psychoneurosis Whether this phenomenon is due to the abnormal behavior of the peripheral vasomotor system as evidenced by the cold cyanotic hands of these patients, or whether the delay may be due to other factors is not as yet determined

Discussion of the method The time elapsing between the arrival of the actve deposit of radium in the right chambers of the heart and its arrival in the arteries about the elbow of the arm may be termed "the crude pulmonary circulation time" The average in sixty-

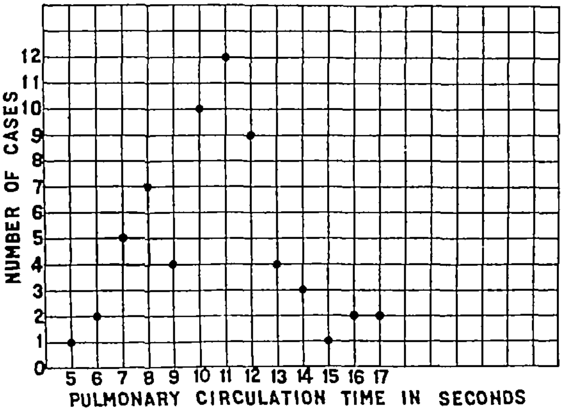

FIG 5 PULMONARY CIRCULATION TIME (CRUDE) IN SECONDS—62 CASES

two measurements was 10 8 seconds This time includes, in addition to the actual pulmonary circulation time, the time of transit through the chambers of the heart and the time taken by the active deposit in traveling from the heart to the antecubital arteries The velocity of arterial blood flow is conspicuously rapid, particularly in vessels as large as the aorta, the subclavian and brachial arteries We have not as yet, by means of the radium active deposit method, actually measured the veolcity of blood flow in arteries Hermann (17) inferred from anatomical and physiological data that the velocity

TABLE 2

Measurements of the pulmonary circulation time and related aspects in normal resting male individuals

Number of measurements	Date	Name	Age	Surface area	Pulse rate	Vital capacity	Vital capacity per square meter	Arterial pressure: Systolic	Arterial pressure: Diastolic	*Venous pressure H_2O	Circulation time: Arm to heart	Circulation time: Arm to arm	Circulation time: Pulmonary	Circulation time per square meter: Arm to heart	Circulation time per square meter: Arm to arm	Circulation time per square meter: Pulmonary
	1926			*square meter*		*cc*	*cc*	*mm*	*mm*	*cm*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*
245	September 24	P S	19	1 68	75	3,250	1,934	130	85	+2 0	6 0	16 0	10 0	3 5	9 5	5 9
250	September 28	Jo D	22	1 64	62	3,900	2,378	140	70	+1 0	7 0	20 0	13 0	4 2	12 1	7 9
253	September 28	G B	25	1 78	69	4,250	2,387	115	80	−2 0	4 75	15 0	10 0	2 8	8 4	5 6
											2 0		10 0	1 1		5 6
254	September 28	I B	21	1 78	74	4,600	2,584	104	65	−1 5	3 0	12 0	9 0	1 6	6 7	5 0
								164	90							
255	September 28	V T	19	1 66	86	4,150	2,500	166	94	0 0	3 5	12 0	8 75	2 1	7 2	5 1
											4 0		11 0	2 3		6 5
256	September 30	E A	23	1 67	97	4,500	2,814	124	94	+1 5	3 0	15 0	12 0	1 7	8 9	7 1
260	September 30	J D	26	1 55	94	3,700	2,387	120	80	−2 0	7 0	16 0	9 0	4 5	10 3	5 8
262	September 30	W C	21	1 99	75	4,700	2,361	114	58		7 5	15 0	8 5	3 7	7 5	4 0
263	October 19	J S	17	1 77	102	3,800	2,146	125	70	+2 0	5 0	15 0	10 0	2 8	8 4	5 6
266	October 19	J P	49	1 55	52	4,100	2,645	125	55	+3 0	5 0	18 0	13 0	3 2	11 6	8 3
269	October 21	T B	24	1 72	86	4,100	2,383	112	74	−1 5	5 5	17 0	11 5	3 1	9 8	6 6
273	October 21	J K	30	1 86	75			118	64	−1 0	6 0	18 0	12 0	3 2	9 6	6 3
274	October 21	R B	20	1 84	80	4,500	2,445	118	76	+1 0	5 0	16 0	11 0	2 7	8 6	5 9
275	October 26	C W	17	1 60	105	3,700	2,312	126	64	+3 0	5 5	12 5	7 0	3 4	7 8	4 3
277	October 26	R P	55	1 71	84	4,250	2,485	112	66		8 0	17 0	9 0	4 6	9 9	5 2
279	October 26	W V	17	1 68	94			98	56	+2 5	3 5	10 5	7 0	2 0	6 2	4 1

280	October 26	A M	38	1.57	69	3,700	2 356	78	54	−1.5	7.0	17.0	10.0	4.4	10.8	6.3
281	October 26	T C.	64	1.97	74	3 600	1,872	132	74	−2.0	4.0	14.0	10.0	2.0	7.1	5.0
285	October 28	J W	48	1.86	70	4 200	2,257	120	62		4.0	17.0	13.0	2.1	9.1	6.9
286	October 28	G Y	24	1.74	98			174	84	+1.3	3.5	10.0	6.5	2.0	5.7	3.7
288	October 28	A G	52	1.55	68	5,500	2 258	120	72	+2.0	6.0	16.5	10.5	3.8	10.6	6.7
289	October 28	J B	43	1.81	92	4,500	2 486	116	62	−1.0	6.0	13.5	7.5	3.3	7.4	4.1
291	October 28	A M	38	1.57	72	3,700	2 356	76	50				17.0			10.8
297	November 4	E. D	62	1.67	62	4 000	2 397	106			6.5	15.5	9.0	3.8	9.2	5.3
299	November 4	T F	65		72			132	76	−3.0	5.5	13.0	7.5			
310	November 19	C W	17	1.60	94	4 300	2 690	114	54	−1.0	5.5	13.0	7.5	3.4	8.1	4.7
311	November 19	M A	23	1.67	76			120	60	+1.6	11.5	20.0	8.5	6.9	11.9	5.0
313	November 23	A. J G	52	1.54	92	3 200	2 129	118	62	+5.5	13.0	25.0	12.0	8.4	16.2	7.8
314	November 23	M A	23	1.67	88			124	76	+19.5	5.5	16.5	11.0	3.3	9.8	6.5
317	November 23	E J	24	2.00	100	5,900	2,950	92	70	−1.0	9.0	17.0	8.0	4.5	8.5	4.0
320	November 23	P S	65	1.63	66			126	76	−3.0	6.5	18.0	11.5	3.9	11.0	7.0
328	December 14	W G	43	1.83	74	4 200	2,295	116	66	+12.0	5.0	17.0	12.0	2.7	9.3	6.7
329	December 14	J B	26	1.71	88	3 800	2,221	118	80	+1.5	6.5	16.5	10.0	3.8	9.7	5.9
	1927															
343	January 18	J C	35	1.59	83	3 100	1 950	106	66	+8.5	5.0	13.0	8.0	3.1	8.1	5.0
344	January 18	E. F	24	1.79	54	4 100	2 290	108	64	+4.0	5.5	16.5	11.0	3.0	9.2	6.1
348	January 19	C. W	35	1.74	112	4 000	2,300	120	58	+8.5	6.0	14.5	8.5	3.4	8.3	4.8
349	January 19	W H.	35	1.72	103	5 150	2 995	114	64	+4.5	5.5	13.5	8.0	3.1	7.8	4.6
350	January 19	M M	35	1.68	111	3 950	2 352	108	70	+6.5	5.0	15.0	10.0	2.9	8.9	5.9
351	January 18	J D	24	1.86	79	4,500	2 419	118	64	+1.5	7.5	19.0	11.5	4.0	10.2	6.1
356	February 9	F A	36	1.66	87	3,250	1 957	102	66	−2.0	5.0	21.0	16.0	3.0	12.6	9.6
364	February 14	J M	21	1.85	94	5,050	2,729	112	80	−1.5	4.0	16.0	12.0	2.1	8.6	6.4
366	February 15	C. C	29	1.70	57	4 500	2 648	106	60	+4.5	10.5	22.0	11.5	6.1	12.9	6.7
367	February 16	C G	25	1.84	50	5 000	2 719	106	66	−1.0	6.5	18.0	11.5	3.5	9.7	6.2
373	February 18	J S	23	1.74	83	4 400	2 527	126	72	+8.0	9.0	19.0	10.0	5.1	10.9	5.2
374	February 18	J S	23	1.74	96	4,400	2 527	126	72	+6.5	11.5	18.0	6.5	6.6	10.3	3.7
375	February 23	J M.	21	1.84	69	4 900	2 662	110	76	−1.5	7.0	21.5	14.5	3.8	11.6	7.8

* To conform to the level of the right auricle, 5.0 cm. should be added to these figures.

TABLE 2—*Continued*

Number of measurements	Date	Name	Age	Surface area	Pulse rate	Vital capacity	Vital capacity per square meter	Arterial pressure		*Venous pressure H_2O	Circulation time			Circulation time per square meter		
								Systolic	Diastolic		Arm to heart	Arm to arm	Pulmonary	Arm to heart	Arm to arm	Pulmonary
	1926			*square meter*		*cc*	*cc*	*mm*	*mm*	*cm*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*
378	February 23	J M	21	1.84	66	4,900	2,662	110	76	−1.0	8.0	19.0	11.0	4.3	10.3	5.9
380	February 23	J G	54	1.78	63	3,500	1,967	165	80	+6.0	11.5	22.0	10.5	6.4	12.0	5.9
382	February 26	P M	21	1.57	67	4,100	2,611	126	64	−1.0	4.5	15.5	11.0	2.8	9.8	7.0
383	February 26	P M	21	1.57	76	4,100	2,611	126	64	−0.5	6.5	18.5	12.0	4.1	11.7	7.6
385	March 9	R P	24	1.84	54	4,700	2,555	122	72	+6.5			16.0			8.7
386	March 9	J R	27	1.91	71	5,150	2,690	114	74	+3.0	11.0	22.0	11.0	5.7	11.5	5.7
388	March 11	E C	33	1.67	63	4,500	2,695	120	74	+5.0	9.0	21.0	12.0	5.3	12.5	7.1
390	March 16	A W	22	1.66	60	4,200	2,529	106	68	+18.0	14.0	26.0	12.0	8.4	15.6	7.2
391	March 16	F D	41	1.62	55	3,650	2,251	94	50	+3.5	13.0	25.0	12.0	8.0	15.4	7.4
392	March 16	A W	22	1.66	63	4,200	2,529	106	68	+6.5	6.5	20.5	14.0	3.9	12.3	8.4
394	March 16	J F	31	1.71	125	3,700	2,162	118	74	−2.0	2.5	8.0	5.5	1.4	4.6	3.2
395	March 16	V F	46	1.74	70	3,350	1,925	124	72	−4.0	6.5	20.5	14.0	3.7	11.7	8.0
400	March 21	H B	36	1.51	78	2,900	1,921	112	60	−2.0	7.0	20.0	13.0	4.6	13.2	8.6
401	March 21	W C	51	2.13	72	3,400	1,596	126	80	+4.5	9.0	21.0	12.0	4.2	9.8	5.6
402	March 21	H B	36	1.51	79	2,900	1,921	112	60	−1.5	6.0	21.0	15.0	3.9	13.9	9.9
416	April 21	J Q	46	1.70	64	3,350	1,970	128	82	−1.0			17.5			10.3

* To conform to the level of the right auricle, 5.0 cm should be added to these figures

of blood flow in the aorta of man may be 144 to 216 mm per second R Tigerstedt (18), basing his estimate on different anatomical data, states that in the aorta it is from 75 to 90 mm per second Although no reliable data concerning the velocity of blood flow in the arteries are available, the time of transit through the large arteries must be relatively short compared to the pulmonary circulation time and the variations in arterial velocity from normal person to normal person must be relatively small

Actual measurement of the time of entrance of the active deposit into the left chambers of the heart has not so far been possible Fortunately, as will be shown, measurement of the velocity of the venous blood to the right chambers of the heart affords a valuable basis for estimating the velocity of the arterial blood flow from the left ventricle to the antecubital arteries In general, the volume blood flow into the right auricle through the inferior and superior vena cava must equal the volume of blood flowing through the systemic aorta in a corresponding interval of time Since the total cross sectional area of the big veins near the heart is about twice that of the root of the aorta, the velocity of the blood in the great veins will be approximately half that of the aorta Similar considerations apply to the relation between other large veins and arteries If the path from the point of injection to the right heart is considered analogous to the path traversed by the active deposit from the left chambers of the heart to the antecubital region of the other arm, as it is in our tests, the circulation time of the venous path will in general be twice as long as the circulation time of the analogous arterial path We have therefore taken half the general average of the venous circulation time to the right chambers of the heart and subtracted it from the "crude pulmonary circulation time" to give the "derived pulmonary circulation time" The arterial velocity correction is 3 3 seconds (that is to say, half the venous velocity time of 6 6 seconds), which subtracted from the general average crude pulmonary circulation time (10 8 seconds), leaves 7 5 seconds as the average derived pulmonary circulation time. This time measures the time necessary for the radium active deposit to flow through the chambers of the heart as well as through the pulmonary circulation, and may therefore vary to a slight degree according to the phase of the cardiac cycle in which the active deposit enters the auricles

and ventricles If the active deposit enters the auricle just before ventricular systole the time lost in the heart will be practically nil, whereas if the radium active deposit enters the auricle at the beginning of venticular diastole the time lost in the heart may be one second if the heart rate is approximately sixty Since similar considerations apply to both sides of the heart, it is conceivable though hardly probable, that the circulation time might be prolonged nearly two seconds Since the time lost in the heart may vary from 0 to 2 seconds, one may consider one second as the average time of transit through the chambers of the heart *One second, therefore, should be subtracted from the* derived pulmonary circulation time to give the actual pulmonary circulation time In our observations, then, 6 5 seconds measures the average time necessary for the active deposit to appear in the left auricle after its previous entrance into the pulmonary artery

RESULTS

The significance of the pulmonary circulation time and its relation to the minute volume output of the heart and to the amount of blood in the lungs As stated above, the pulmonary circulation time refers to the time necessary for a given particle of blood to appear in the left auricle after its previous entrance into the pulmonary artery This time measures the interval necessary for the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection If the vascular pathways were all equal the pulmonary circulation time would signify the interval necessary for the displacement of the blood in the lungs, and would be a measure of the mean velocity On the other hand, if there are considerable variations in the different pathways of the pulmonary circuit, or if there is a hastening on of the central stream, the pulmonary circulation time would have no necessary relation to the amount of blood displaced in the lungs, and its significance would therefore be lessened The work of G N Stewart (4), as well as some observations discussed in a previous communication (10), indicate that the pulmonary circulation time is an index of the mean pulmonary blood velocity G N Stewart found that, following the injection of dyes into the external jugular vein, there was no stringing out of the dye after it had traversed the pulmonary capillaries and had entered the

carotid artery This observation lends support to the concept of the equality of the available pulmonary vascular pathways Similarly, G N Stewart has pointed out (19) that the mean pulmonary circulation time bears a definite relation to the quantity of blood in the lungs and the minute volume flow through the lungs This relation may be expressed by the formula $V = Q\frac{60}{T}$, where V is the volume output of the heart per minute in liters, Q is the quantity of blood in the lungs in cubic centimeters, and T is the mean pulmonary circulation time in seconds If two of these unknown quantities are measured the third can be ascertained According to the relation expressed by the above formula, the pulmonary circulation time will vary directly with the amount of blood in the lungs and inversely with the minute volume flow through lungs An increase in the pulmonary circulation time signifies a preponderant increase in the amount of blood in the lungs compared to the minute volume output of the right ventricle Since the pulmonary circulation time reflects changes in either or both these two factors it is of the utmost importance in expressing their balance under various conditions in health and disease. The use of the pulmonary circulation time as T in this formula depends on the assumption that the pulmonary circulation time is identical with the mean velocity On the other hand, if the vascular pathways are dissimilar or if there is considerable hastening on of the axial stream, T, in the formula would be too low and the amount of blood in the lungs would become impossibly small

The general average of the actual pulmonary circulation times presented in the preceding tables is 6 5 seconds The table below (table 3) is a summary of measurements of the minute volume output of the heart in normal males lying at rest as found by various observers Measurements of the minute volume output of the heart, available from the literature, performed with the subjects in sitting position are not comparable to our data

The average of the minute volume output found by these two different methods in normal resting males is 6 38 liters Applying the above mentioned equation $V = Q\ \frac{60}{T}$, $6\ 38 = Q\ \frac{60}{6.5}$ or Q, the amount of blood in the lungs equals 589 cc It is interesting in the

light of this finding which is the first approximation by actual measurements during life of the amount of blood in the lungs of man, to learn

TABLE 3

Minute volume of heart in normal males lying at rest as obtained from literature

Subject	Minute volume output	Observers
	cc.	
A. V B	5 45	H Field and A. V Bock (20, 21)
H. F	10 90	
A. C R	7 14 (8 9, 5 38)	
J R. L	9 00	
W A Mc	8 10	
T M M	6 70	
S A O	8 10	
F W L	6 55	
C M J	7 30	
F T H	4 81	
J M F	7 17	
W L McK	6 72	
W B C	7 28	
P D	7 80	
A. M B	8 34	
J C E	8 51	
M E M	5 13	
M F H	6 63	
M A S	7 46	
S L W	5 35	
H. P S	9 03	
H N S	5 90	
A. K	6 63	
E F G	9 23	
G C R	4 70	
Average	7 19	
Male	5 65	Lindhard (22)
Male	5 30	
Male	7 20	
Male	4 20	
Average	5 57	

the amounts surmised by various observers in the past Spehl and Desquin (23) found in eight rabbits that the pulmonary blood volume at the end of inspiration was 8 3 per cent of the total blood volume

Y Kuno (24), working on heart lung preparations of dogs and calculating total blood volume as 7 per cent of the body weight, found that the volume of the blood in the lungs varied between 8 8 and 19 6 per cent with an average of 12 per cent of the total blood volume G N Stewart (4) found in two dogs in which both sides of the heart were obstructed simultaneously, that the lungs contained 21 and 18 6 per cent of the total blood volume Assuming, as did G N Stewart, that, as in the case of animals, the total blood volume of man is about one thirteenth of his body weight, and taking the average weight of the subjects as 70 kilos, the total blood volume would be 5 4 liters in which case 589 cc would represent 11 per cent of the total blood volume This observation is of importance not only in giving information in regard to the amount of blood in the lungs but also because it confirms the validity of the pulmonary circulation time as a measure of the mean velocity and at the same time indicates that the available pulmonary pathways are approximately equal For if the mean velocity were much slower than the actual pulmonary circulation time observed, the value of Q would become impossibly large. Our finding of 589 cc of blood as the average amount of blood in the lungs of man is in accord with the results of previous investigations on animals

The relation of systemic blood pressure to the normal pulmonary circulation time The effect, in animals, of changes of the systemic arterial blood pressure upon the pulmonary circulation of animals has been studied by various observers. Fühner and Starling (25) working with the heart lung preparation, in which the cardiac rate and venous inflow were controlled, noted, in apparently vigorous hearts, that every elevation of systemic pressure caused a corresponding increase of pressure in the left auricle, the pulmonary artery and even in the right auricle Similarly, Cloetta and Staubli (26) observed that compression of the thoracic aorta always caused increased lung volume and elevation of pulmonary arterial pressure. Straub (27) found that increased peripheral arterial resistance always produced passive pulmonary congestion as indicted by increased lung volume and increased left auricular pressure Bradford and Dean (28) similarly observed that temporary compression of the aorta, or increased vasoconstriction, caused slight elevation of pulmonary arterial pressure. A rise of pres

sure in the pulmonary circulation would not, of course, cause an increased velocity of blood flow unless the "head on" pressure, i e, the pressure gradient, were greater On the contrary, a simple increase in pressure, by distending the elastic pulmonary bed and increasing the amount of blood in the lungs, would lead to a lengthened pulmonary circulation time It seemed of interest to compare the pulmonary circulation times in those individuals who showed the highest and lowest blood pressures (table 4)

These results show no evident relation between normal variations in pulmonary circulation time and normal variations in systemic blood pressure Back pressure effects either do not occur normally in man, or if they do occur, any increase in the amount of blood in the lungs is

TABLE 4

Blood pressure and pulmonary circulation time

Patient Number	Blood pressure		Pulmonary circulation time	Patient Number	Blood pressure		Pulmonary circulation time
	Systolic	Diastolic			Systolic	Diastolic	
	mm Hg	*mm Hg*	*seconds*		*mm Hg*	*mm Hg*	*seconds*
255	166	94	5 5	279	98	56	3 5
286	174	84	3 0	280	78	54	6 5
250	140	70	9 5	317	92	70	4 5

attended by a proportionate increase in the minute volume flow of blood

Conditions which may account for the variations in pulmonary circulation time of healthy men The pulmonary circulation time may conceivably be influenced according to the phase of respiration during which the active deposit enters the heart and pulmonary vessels We have not had the opportunity to investigate this particular point although repeated measurements in the same person show that such an influence, if present, can hardly be of clinical or physiological significance This is in accord with the observations of E K Marshall (29) who found that changes of 100 per cent or more in the ventilation of the lungs were not accompanied by changes in the minute volume output of the heart in trained unanesthetized dogs

The relation between the ventricular rate of the heart and the velocity of blood flow through the lungs The data in table 5 indicate that an

increased ventricular rate is associated with a slightly though definitely increased velocity of blood flow, although this relation does not obtain in each instance In this connection patient J F (391, table 2), who was suffering from post traumatic neurosis, is of particular interest Although he was coöperative his pulse rate was 125 and he showed the signs of excitement The venous flow time was 2.5 seconds and the crude pulmonary circulation time was 5.5 seconds Applying the considerations previously discussed, but using the patient's own venous time and ventricular rate, because of the con-

TABLE 5

Ventricular rate and pulmonary circulation time

Ventricular rate 90+			Ventricular rate 0–		
Patient number	Pulse	Pulmonary circulation time (crude)	Patient number	Pulse	Pulmonary circulation time (crude)
		seconds			*seconds*
256	97	11.5	250	62	13
260	94	9	253	69	10
263	102	10	266	52	13
275	105	7	280	69	10
279	94	7	285	70	13
286	98	6.5	288	68	10.5
289	92	7.5	297	62	9
310	94	7.5	320	66	11.5
313	92	12			
317	100	8			
	125	5.5			
Average	96.8	8.4		65	11.2

spicuous deviation from the average, his actual pulmonary circulation time was 3.8 seconds This is the shortest actual pulmonary circulation time so far observed In our previous study (7) of the normal arm to arm circulation time an increase in the pulse rate was likewise associated with a slight but definite increase in the velocity of blood flow

The influence of age on the velocity of blood flow through the lungs According to the measurements of the pulmonary circulation tabulated (table 2), the velocity of blood flow through the lungs showed no constant relation to the age of the patient This is in accord with our

previous observations on the arm to arm circulation times according to which the velocity of blood flow expressed the actual condition of the circulation independent of the age of the patient In a few young persons, in whom the ventricular rate was elevated, the velocity of blood flow was somewhat increased

The influence of the venous pressure on the velocity of blood flow through the lungs Whether high venous pressure as observed in the antecubital vein of the arm is associated with an increase in the velocity of venous blood to the heart and through the lungs depends on the cause of the increase in pressure Were the increase in pressure due to obstruction or pressure on the vein, or to vasomotor constriction with consequent undue closure of the venous valves or to circulatory failure, one would expect a retardation in the velocity of blood flow For in all these instances the pressure increase is due to lessened outflow from the vein rather than to increased inflow In certain persons who appeared perfectly normal, though somewhat excitable, the venous pressure was unusually high and the velocity of venous blood flow to the right heart chambers was considerably retarded (nos 311, 313, 314, table 2) In a few instances this venous slowing has been associated with undue prolongation of the pulmonary circulation time

The relation between the surface area and the velocity of blood flow The heat production and also the vital capacity of the lungs bear definite relations to the surface area in man These measurements express a relation between absolute quantities and surface area The velocity of blood flow as reported in these communications does not refer to velocity of flow in actual units of time and distance but rather to the time necessary for the active deposit of radium to travel between certain arbitrarily chosen points If, in large persons, the distance between the two arbitrarily chosen points were proportional to the increase in surface area and the velocity of blood flow in absolute units of time and distance were to remain unchanged, increased surface area would be associated with increase in the pulmonary circulation time That the circulation times as measured by our method did not show any definite relation to the surface area indicates that the time of transit is independent of the distance between the arbitrarily chosen points

SUMMARY

1. The radium C method makes possible for the first time the measurement in man of the velocity of blood flow through the lungs.

2. The method described measures also the velocity of the venous blood from the arm to the right chambers of the heart.

3. The crude pulmonary circulation time in sixty-two measurements on normal resting individuals varied from five to seventeen seconds. The average crude pulmonary circulation time was eleven (10.8) seconds.

4. The circulation time of the venous blood from the right elbow to the right auricle varied from two to fourteen seconds with an average of seven (6.7) seconds.

5. Repeated measurements in the same individuals showed a maximum variation in the crude pulmonary circulation of three and a half seconds with an average of two seconds while the maximum variation in the venous flow time was seven and a half seconds, with an average of three seconds.

6. The variations in the velocity of blood flow through the lungs in the same individuals at different times and in different individuals are less than that observed in the velocity of the venous blood of the arm.

7. No definite relation was observed between velocity of pulmonary blood flow and age of the patient.

8. With a conspicuous increase in the pulse rate there is a slight but definite increase in the velocity of blood flow through the lungs.

9. Normal variations in systemic arterial or venous blood pressure bear no relation to normal variations in velocity of blood flow through the lungs.

10. The average actual pulmonary circulation time observed by us was 6.5 seconds, the average minute volume flow through the lungs as observed by others was 6.38 liters. According to the formula $Q = \frac{TV}{60}$ and applying the pulmonary circulation time as mean velocity, T, the amount of blood in the lungs of man averages 589 cc. or 11 per cent of the total blood volume.

11. The fact that the proportion of blood in the lungs of man so calculated conforms to that found experimentally in animals indicates that the pulmonary circulation time is a measure of the mean

velocity of blood flow through the lungs and that the available pulmonary pathways are about equal

We wish to thank the General Electric Company of Schenectady, New York, and, in particular, Dr William D Coolidge and Dr Clarence W Hewlett for their kind assistance and advice We are also indebted to Mr A A Clokey of Rutherford, N J for the recording galvanometer and to Mrs Elizabeth Hall for technical assistance

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PROCEEDINGS OF THE NINETEENTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION HELD IN ATLANTIC CITY, NEW JERSEY, MAY 2, 1927

Dr John Howland

Born 1873 Died 1926

Since the last meeting of the Society we have suffered the loss of another of our founders John Howland He was born in New York City in 1873 In his undergraduate days at Yale he displayed qualities which were later to distinguish him His social success was due to an attractive capacity for meeting his fellows, and as an athlete he learned to do things well and ranked as one of the best tennis players in the country He studied medicine and graduated in 1897 from the New York University and Bellevue Hospital Medical School, served his internship in Presbyterian Hospital, and was later on the staff of the New York Foundling Hospital As an assistant of the late Dr L Emmett Holt he was inspired to pursue the study of pediatrics He was called from his post at the College of Physicians and Surgeons to become Professor of Pediatrics in the newly organized school of Washington University, St. Louis, and shortly after was appointed Chief of the Department of Pediatrics at Johns Hopkins Medical School, which position he held until his death It is no exaggeration to state that he founded the first real University Department of Pedatrics in this country, and hence his influence will be long felt in the development of this important branch of medicine He himself regarded this as his most important contribution But we, as fellow members of a Society in which he took such a leading part, have derived great inspiration and instruction from the successive stages of his career as a clinical investigator In his younger days he made contributions in morphology, physiology and pharmacology Finally, with the trend of the times, he foresaw the possibilities of applying chemical methods to the solution of the problems of disease, and his contributions to the subject of rickets stand as milestones in medicine But with all of these studies he was first

and foremost a clinician and teacher His great capacity for friendliness and his sympathy made his influence felt far beyond the circle of his immediate daily associates He combined a variety of abilities as few men do, and because of his stimulating qualities of mind, was the ideal head of a clinical department and an ideal member of this Society

For all these reasons and because of the affection of its members for him, the American Society for Clinical Investigation wishes to place on record its feeling of great loss caused by his departure from us

The Effect of Fever on the Basal Metabolism, Insensible Perspiration, and Skin Temperature of a Child By FRITZ B TALBOT, Boston, Mass

A case, J E , aged nineteen months had regular and repeated elevations of temperature which could be predicted, prepared for, and studied These febrile attacks persisted for several weeks and finally disappeared Repeated physical examinations and numerous laboratory tests failed to reveal their cause After a long illness of several weeks he was discharged well from the hospital

The basal metabolism, insensible prespiration, and skin temperatures were measured at various times and compared with the height of the fever The relation of the basal metabolism to the body temperature confirmed the findings of DuBois and his co-workers

The metabolism increases in the same manner that it does in the adult, and the variation from the average is no greater than that found by DuBois (1) This case indicates that the metabolism of a young child is affected by fever in the same way as in the adult

The "insensible perspiration" was obtained by weighing an infant for periods of one-half hour on delicate balance scales in the open room and observing the loss in body weight It is seen to increase with increasing body temperature in the same manner as does the basal metabolism The insensible perspiration shows a definite relationship to the basal metabolism Such a relationship has also been found in three cretins before and after administration of thyroid extract and in a series of normal infants (unpublished data) now being studied

The skin temperature was measured by a thermo-couple and a portable string galvanometer as devised by Benedict (2) The temperature of various prescribed points was taken underneath the clothing The temperature of the trunk is higher than that of the extremities, but both tend to increase in a corresponding manner with the body temperature

The skin temperature under the clothing shows that there is also a regular relationship between the external skin temperature and the rectal temperature during fever This relationship apparently also holds during the fever of lobar pneumonia A series of skin temperatures now being collected indicate that

this measurement is a very valuable adjunct in the study of heat elimination from the body

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The Effect of Iodin in Cases of So-called Toxic Adenoma By JOHN B YOUMANS and (by invitation) RUDOLPH H. KAMPMEIER, Ann Arbor, Mich

The favorable effects of iodin in exophthalmic goiter suggested to the authors that should similar effects be obtained in cases of "toxic adenoma" they would constitute evidence for the fundamental identity of these two conditions The general belief in the concept of two entirely distinct forms of thyrotoxicosis is emphasized by the common acceptance of the view that iodin is harmful and contraindicated in cases of toxic adenoma

Three years ago we began the use of iodin in unselected cases of "toxic adenoma " The cases were hospitalized and following a period of observation under medical regime iodin was administered (usually Lugol's solution, minims V, three times daily), and careful observations made including basal metabolism determinations A series of similar cases not treated with iodin and of exophthalmic goiter treated with iodin was studied

Satisfactory data were obtained in 30 cases of 'toxic adenoma" treated with iodin, and somewhat less complete data in 48 more The results obtained indicate that the response to iodin of cases of "toxic adenoma" previously untreated with iodin is essentially the same as that of exophthalmic goiter No instance of harmful effect was observed Characteristic escape from iodin effect following discontinued or prolonged administration of iodin was observed

The Relation between Seizures in Epilepsy and the Acid Base Balance in the Blood By WM. G LENNOX, Boston, Mass

A study has been made of 4 epileptic patients, each having constantly many seizures a day In conditions of alkalosis induced by administration of alkali or over ventilation, seizures were much more frequent In conditions of acidosis induced by fasting, ketogenic diet, administration of acid forming salts or by rebreathing, seizures were much less frequent Because curves signifying acid base changes in the blood and frequency of seizures did not maintain a constantly parallel course, associated changes in nerve cells such as the tension of oxygen, the equilibrium of electrolytes, or the permeability of cell membranes may play a more fundamental part Because in conditions of acidosis tendon reflexes were diminished we believe that acidosis acts by causing a decrease in the irritability of nervous tissues Although these observations do not offer immediate hope of therapeutic results in the treatment of adult epileptics, they do bring us nearer to an understanding of the mechanism involved in seizures

The Regulation of Circulation, Studies on the Mechanism Whereby Anoxemia Causes an Increased Cardiac Output By G CANBY ROBINSON, and (by invitation) ALFRED BLALOCK, TINSLEY R HARRISON, and COBB PILCHER, Nashville, Tenn

Severe anoxemia of short duration has been demonstrated to cause an increased minute cardiac output in morphinized dogs and "trained" unnarcotized dogs The present work is concerned with an attempt to study the mechanism in the body responsible for this apparently compensatory reaction

Observations have been made as to the "anoxemic threshold," i e , the mildest degree of anoxemia which leads to an increased cardiac output In experiments of short duration, this value seems to lie in different normal animals between 65 and 85 per cent of arterial saturation Studies were made of the various factors which might influence the circulatory response to anoexmia

(a) *The adrenal glands* are not necessary for this reaction as anoxemia causes increased cardiac output in adrenalectomized dogs

(b) *The central nervous system* After removal of the stellate ganglia and thoracic sympathetic trunks the response to anoxemia is unchanged After double vagotomy, anoxemia usually causes an increased cardiac output but the degree of increase is apparently less than in animals with intact vagi Results up to the present time have led to the tentative hypothesis that deficient oxygenation of the coronary blood stimulates the cardiac output by a direct myocardial action but that the sensitiveness of the myocardium to this stimulus is partially controlled by the medulla through the vagi Changes in the peripheral circulation have not been adequately studied as yet, and must be evaluated before this problem can be regarded as settled

Pulse Wave Velocity under Varying Conditions in Normal and Abnormal Human Cardiovascular Systems By ROY H TURNER (by invitation) and GEORGE R HERRMANN, New Orleans, La

The study of the velocity of the pulse wave under suddenly varied conditions of pressure has been made easily possible by a helium lamp recording apparatus recently devised by Dr Turner

Patients whose pulse wave velocity was studied by this method have been grouped into five classes as follows

1 Normal individuals, among whom the highest P W V was 6 meters per second

2 Cases of hypertension without arterial changes, who showed increases as follows *one, 40 per cent, three, 80 per cent, two, 100 per cent*

3 Cases of hypertension with large tortuous, slightly thickened arteries, two of which showed a normal P W V , one a 33 per cent, two a 100 per cent and one a 125 per cent increase

4 Cases of hypertension with large, tortuous, definitely thickened vessels

showed one a 25 per cent and three a 100 per cent increase with one increase of 200 per cent in a case with marked calcareous deposits in the arteries

5 Patients with large, dilated and thickened vessels with normal blood pressure showed one a 25 per cent and three a 40 per cent increase with one 175 per cent increase in a patient with the most advanced corrugating sclerosis

The data now available indicate that there are other factors aside from elasticity and blood pressure that influence pulse wave velocity The change in calibre of the artery, especially enlargement, may be a most important compensatory factor resulting in alterations in P W V Reducing the pressure actually increased the P W V in two instances The method gives a definite index of the functional efficiency of the peripheral arteries

The Effect of Digitalis upon the Pulse Rate and Circulatory Minute Volume of Normal Human Subjects By C SIDNEY BURWELL and (by invitation) DEWITT NEIGHBORS and E M REGEN, Nashville, Tenn

One year ago Harrison and Leonard demonstrated a fall in cardiac output of the dog after the administration of "therapeutic" doses of digitalis This observation differed so profoundly from those on the perfused and isolated heart, and the difference had such significance that it was felt essential to determine whether or not digitalis produced a similar effect in man

Accordingly digitalis leaf of known potency was administered to a series of normal men, and the cardiac output and "basal" pulse rate observed before and after its administration All observations were made in the morning, with the subject in the post-absorptive condition and at complete rest The cardiac output was determined by the method of Field, Bock Gildea and Lathrop By the "basal pulse rate" is meant an average of the 8 to 12 half minute counts made during each determination of cardiac output The usual procedure was to train the subject in the respiratory maneuvers necessary for the determination on one or two occasions before his cardiac output was actually observed The control observations were then made on successive days until an apparent normal level was established If as was often the case, the first one or two determinations were higher than subsequent ones, these high figures were discarded

Digitalis leaves were given by mouth The initial dose was usually 1 gram and this was followed by smaller doses at intervals of twenty four hours until a stage of undoubted digitalis effect was reached as judged by the changes in pulse, cardiac output and electrocardiogram and by the occurrence of nausea. Observations of cardiac output and basal pulse rate were made daily during the period of administration and of maximum effect and at slightly longer intervals during the recovery period Such studies were carried out upon five individuals

Following the administration of digitalis there was in each case a drop in the basal pulse rate of from 8 to 12 beats per minute After the cessation of digitalis administration there was a gradual return to the predigitalis level in approximately 3 to 4 weeks Some drop occurred in each case after the initial dose of the drug

The effect on cardiac output was in general similar in all five individuals stu(Each one showed a diminution in output immediately following administratio the drug This "initial" drop averaged 16 per cent of the previous cardiac out As the administration of the drug was continued and nausea supervened cardiac output rose until it was only 6 per cent below the original average drug was then discontinued Following this "toxic period" there was a "sec ary' drop to 18 per cent below, and after this a gradual return to 4 per cent than the original normal The output per beat was diminished as well as pulse rate

These studies include a small number of individuals but a considerable nur of generally concordant observations

The following conclusions may be drawn

1 Digitalis diminishes the basal pulse rate and this diminution persists for t weeks and upwards

2 The cardiac output per minute is not increased by digitalis On the cont it shows a definite diminution, due not only to the fall in pulse rate but also lessening of the output per beat

The Velocity of Pulmonary Blood Flow in Health and Disease By HERRMAN BLUMGART and (by invitation) SOMA WEISS, Boston, Mass

The radium active deposit method enables one to study for the first time velocity of blood flow through the lungs of man Active deposit of radiu injected into the cubital vein of one arm When the active deposit reaches right chambers of the heart the gamma rays produce an ionization current wl when amplified, is automatically registered by an appropriate recording de Similarly, the time of arrival of the active deposit in the arterial vessels about elbow is automatically recorded The time that elapses between the instar injection and the time of arrival of the active deposit in the right chambers of heart measures the velocity of venous blood from the arm to the heart The time that elapses between the arrival of the active deposit of radium in the right h chambers and the arrival in the arteries about the elbow of the other arm g after the application of a standard correction, a measurement of the velocit blood flow through the lungs

In fifty normal persons in whom the venous pressure and vital capacity normal, the pulmonary circulation time ranged from four and a half to seven seconds The average time was eleven seconds Pulmonary circulation t above seventeen seconds were always associated with pathological condition the circulation In general, the slowing of the venous blood flow and of pulmonary blood flow corresponded to the degree of circulatory failure, in most severely decompensated patients the venous circulation time being as as thirty-four seconds and the pulmonary circulation time sixty-eight seco In the presence of emphysema the velocity of blood flow through the lungs be normal

In normal persons the administration of digitalis to the point of toxicity produces no demonstrable effect on the velocity of pulmonary blood flow, whereas in cardiac patients in whom there was definite clinical improvement following digitalization the velocity of blood flow through the lungs was increased

According to the formula developed by G N Stewart, that $V = Q \frac{60}{T}$ where V equals the minute volume flow through the lungs Q signifies the quantity of blood in the lungs and T is the mean velocity of pulmonary blood flow, if two of the three factors are known the third can be calculated In fourteen individuals actual measurements of both the minute volume output and of the pulmonary circulation time were accomplished Using the pulmonary circulation time as the mean velocity in this formula, the quantity of blood in the lungs was calculated and found to be approximately 18 per cent of the total blood volume This is in accord with the estimates of physiologists based on observations in animals It is noteworthy that substitution of the circulation time for the mean velocity secures such a plausible estimate, for if the circulation time were not closely comparable to the mean velocity the calculation would have produced an estimate wholly unreasonable

The Behavior of Pulmonary Vessels as Determined by Direct Observation in the Intact Chest By JOSEPH T WEARN and (by invitation) ARTHUR C ERNSTENE, J S BARR and W J GERMAN, Boston Mass

A method has been devised which permits study of the pulmonary circulation in the cat by direct observation and under physiological conditions

Under amytal anesthesia the parietal pleura of the eighth interspace is exposed in the right anterior axillary line over an area measuring 0 75 by 1 5 cm Through an abdominal incision a similar pleural window is prepared by removing the muscle fibres of the diaphragm immediately opposite the window in the chest wall The animal is now curarized, and the lungs are held stationary in the normal inspiratory position by means of a gentle blast of air through a small catheter introduced to the bifurcation of the trachea By means of the diaphragmatic window a beam of light is passed through the tip of the lower lobe of the lung at sufficient intensity to permit direct observation of the pulmonary vessels with a microscope at the outer window, using a magnification of 110 diameters Carotid pressure tracings have been made in all experiments It has been possible with this method to observe the number and calibre of the capillaries and of the smaller arteries and veins In addition it is possible to detect relative changes in the velocity of blood flow through these vessels

The number of active capillaries has varied greatly in different preparations In some instances there have been but one or two capillaries per air sac. In the majority of experiments, however, there have been six to eight capillaries per air sac while in a few instances the capillaries have been so numerous and have formed such a close meshed network that accurate counts were impossible.

Furthermore, the number of active capillaries in an individual air sac has been observed to vary from time to time Capillaries have been seen to disappear and reappear without changes in the systemic blood pressure

Small intravenous doses of adrenalin have been given in a few experiments and, as the systemic blood pressure rose, a variable number of new capillaries has been seen to appear in the air sacs under observation Further studies upon the effect of this and other drugs are now under way

Vasomotor Mechanism in Cerebral Circulation By STANLEY COBB, and (by invitation) H S FORBES and H G WOLFF, Boston Mass

By direct examination of the cerebral vessels (pial) of the cat through a tightly sealed window so constructed as to permit the removal of air and the injection of fluids, accurate calibrations of the vessels by micrometry and photography have been made

It has been determined that the cerebral vessels may show changes in diameter, consistent with mere passive expansion or collapse, following abrupt rises or falls in arterial pressure In addition to these passive changes in caliber, the arteries show changes exactly opposite in direction to the above These latter changes can be brought about by stimulation of constrictor or dilator nerves, and by other means

The conclusion seems justified that the cerebral circulation is not regulated wholly from a distance by splanchnic or general systemic vaso-constriction and dilatation (passive) but is also dependent upon an active vasomotor mechanism within the cerebral vessels themselves

The Circulating Blood Volume in Diabetes Mellitus and Diabetic Acidosis By GEO A HARROP, JR, and (by invitation) H C CHANG, Baltimore, Md

A critical study has been made of the carbon monoxide method for the determination of the circulating blood volume in man, and particularly of the extent to which the gas is mixed in the circulating blood and the loss to the extra vascular hemoglobin Series of estimations using prolonged experimental periods and taken at different stages during continuous exercise have indicated that the errors involved from these factors under controlled conditions is slight A more delicate technique has been developed for the quantitative estimation of carbon monoxide in the blood

The method has been applied to a study of the relationship existing between hyperglycemia, the occurrence of polyuria and polydipsia, acidosis, clinical dehydration, and the circulating blood volume in diabetes mellitus In patients with marked hyperglycemia, thirst and polyuria, and even with rather marked dehydration, the circulating blood volume is high as compared with the normal when calculated on the basis either of cubic centimeters of blood per kilogram of body weight or per square meter of surface area In patients with acidosis, even where the plasma bicarbonate capacity is as low as twenty volumes per cent, no

blood volume values have been found below the lowest obtained in normal subjects Significant diminution, however, of the plasma volume has been found in three such cases in which the hematocrit determinations and erythrocyte counts showed an increased red cell volume The blood volume in such cases under insulin and dietary treatment later again became high No determinations have been made in cases of actual coma Patients under dietary treatment with or without insulin where hyperglycemia has not been present over long periods have normal circulating blood volumes and plasma volumes.

The circulating blood volume, then, in severe and in untreated diabetes, when associated with polyuria, polydipsia and hyperglycemia appears to be increased, notwithstanding the presence of clinical dehydration Where acidosis supervenes, the blood volume is diminished but we have not even in this condition found abnormally low blood volumes

Synthalin By Elliott P Joslin, Boston, Mass

The extraordinary improvement of the modern diabetic with diet and insulin makes it exceedingly difficult to estimate the value of any new method of treatment Particularly is this true with patients who have been under observation for only a few years

During the last three months synthalin has been employed with eight of my cases but only with one of these cases, case no 4306, for the greater portion of the time With this case the insulin has been reduced from 28 to 16 units daily and the carbohydrate, protein and fat in the diet maintained at their previous levels I have tried to omit six more units, the evening dose, but as yet without success as glycosuria appears With another patient, case no 5900, insulin, 13 units, has been totally replaced with synthalin and the patient's blood sugar for an interval of two weeks has fallen nearly to normal. To the former patient 50 mgm. synthalin were given daily for two days and then as a rule omitted for one or two days, and the cycle repeated, to the latter 30 mgm synthalin were given daily for three days and then omitted for a day and then repeated None of my other cases are as convincing A third patient, case no 5974 became sugar free with diet and insulin the insulin was then omitted and he too remained sugar free with synthalin but he was a recently treated case and might have behaved so without synthalin One patient, case no 3483, with hyperthyroidism did better after operation with synthalin, replacing insulin, than one would have expected without insulin, and this observation is of some significance because I have experience thanks to F H Lahey, with 75 cases of diabetes with hyperthyroidism One patient case no 5608, disliked synthalin, two others, old ladies, cases no 1494 and 3751, with a few grams of sugar in the urine appeared to be more nearly sugar free and more consistently sugar free when synthalin was used

Synthalin did not act efficaciously in one true diabetic, case no 2296, who happens to have a low blood sugar threshold but I am yet in hopes for better results

Synthalin caused nausea and even vomiting in our first case Subsequently when the drug was resumed no nausea appeared, but the dosage, 4 × 25 mgm in two days, was spread over a few more hours or even several days

Synthalin appeared to work better after successive turns of two days at a time with a day's interval without the medication

Synthalin acts in diabetes Three milligrams replaced 1 unit of insulin in my first case, if one includes in the effect the two days of medication and the day following as well, and 1 mgm replaced approximately 1 unit in the second case, but in this case perhaps the patient's tolerance was improving

None of my diabetic children and none of my patients with acidosis have been given synthalin

I wish to acknowledge my indebtedness to Professor E Frank of Breslau and to the Messrs Kahlbaum Company for the privilege of using synthalin I believe it is worthy of continued use and that with a better knowledge of it, there will be a group of diabetic cases that can employ it advantageously More important is the probability that it is the forerunner of other and better preparations which one can give by mouth and which to a certain degree will replace insulin

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Hyperinsulinism, from Carcinoma of the Islands of Langerhans By R M WILDER and (by invitation) H N ALLAN and H E ROBERTSON, Rochester, Minn

This case, I can say without exaggeration, is one of the most significant in medical experience Its study yields new knowledge, important in clinical medicine, in physiology and in pathology We were fortunate not only in having the opportunity to conduct a very complete clinical investigation, but also in obtaining the end picture from the pathologists

We are dealing here with a disease that is new in the sense that heretofore it has not been described, namely, carcinoma of the Islands of Langerhans with hyperinsulinism We also possess in this case what is, I think, the first well authenticated instance of a carcinoma of any origin possessing the function of the parent cells The tumor in this case is a cancer by all the commonly accepted criteria of carcinoma and from this cancer a substance has been extracted which, so far as we can tell, has the same physiological action as insulin

The disease in this case existed for a good many years, at least eight, but the picture of excessive insulin action only became evident in 1924 The patient, a surgeon forty years of age, suffered acute abdominal pains in 1918 An exploratory operation at that time revealed no gross pathology, nevertheless a gastroenterostomy was performed In 1921 and again in 1924, the continuance of vague

upper abdominal symptoms brought him to the Mayo Clinic, but no definite diagnosis could be made at either of these examinations Later in 1924, he began to develop acute attacks of weakness while engaged at his morning work and found that he could antidote these attacks by drinking coca-cola or malted milk Then an attack occurred while he was operating, an attack associated with convulsions and loss of consciousness which so closely resembled the clinical picture of a diabetic patient who has been over-dosed with insulin that the thought occurred to the attending doctors to inject him intravenously with glucose This, fortunately, was done and recovery of consciousness followed immediately Thereafter, sugar was taken by mouth at regular intervals, larger and larger doses and shorter intervals being needed until before the time of death he took 65 grams of glucose hourly day and night to prevent hypoglycemia

In July, 1926, an examination was made by Dr Ulrich of Minneapolis who recognized the fact that he had to deal with an unusual clinical picture associated with hypoglycemia but was unable to determine its nature. In November, the patient again consulted the Clinic, arriving at the hospital in a state of collapse which had all the ear marks of hypoglycemic shock and with a blood sugar so low that it could only be determined with difficulty

Our studies and experiments are too extensive to permit of more than partial summarizing At first, we directed attention to the liver, being impressed by the fact that the amount of sugar necessary to prevent hypoglycemia was approximately equal to that which Mann finds to be the requirement for each kilogram of body weight in dehepatized dogs We found, however, that the liver was normal in every function that we could test, amino acids were properly deaminized and urea formed in normal amounts, there was a normal secretion of bile and no retention of pigments We found then that the metabolism was abnormally stimulated and respiratory quotients indicated that the materials burning were made up largely of carbohydrate We obtained evidence also of rapid formation of fat in the fact that the respiratory quotients, after test meals of sugar, rose over unity, to 1.20 This was confirmed by the fact that the patient was gaining weight We found also that the phosphates in the blood would fall with the fall in the blood sugar after test meals, exactly as occurs after injections of insulin and sugar and our opinion of the etiology veered away from the liver to the pancreas and the idea of hyperinsulinism

An exploratory operation was performed on the fourth of December by Doctor Mayo who described a hardening and irregularity of the body and tail of the pancreas and two unusual nodules palpable on the surface of the liver The gall bladder was diseased and this he removed He also took out a small piece of liver The liver thus removed in the middle of an operation with ether anesthesia contained nearly 4 per cent of glycogen This, to judge from experience with dogs, is a high glycogen content and this finding excluded the possibility of the patient's symptoms being due to loss of glycogen function, and together with the other findings at operation, focused attention still more closely on the pancreas

It was proposed tentatively that a carcinoma of the pancreas with metastasis to the liver would explain the clinical picture, and, since the Island tissue and presumably also functioning carcinoma in the pancreas would be under the normal nerve control and, therefore, should not over-function, it was further suggested that the metastasis should be functioning and producing insulin widely On the basis of this tentative diagnosis and with the purpose of inhibiting the functioning of metastatic Island tissue in the liver, Doctor Bowing was asked to use radium over the liver This he did without, however, noticeably affecting the clinical condition The patient finally died not from an attack of hypoglycemia or from cachexia, but apparently from exhaustion

The findings of Doctor Robertson at the necropsy are in entire harmony with the idea of metastatic carcinoma of Islands of Langerhans and evidence of the functioning of this cancer tissue is supplied by Doctor Power who has painstakingly applied Best's technique for insulin extraction both to a portion of the tumor in the liver and to an equal portion of the non-tumorous liver tissue From the non-tumorous liver taken as a control, 33 mgm of material was obtained, one-half of this was injected into a rabbit without appreciable effect From the tumor 57 mgm of material was obtained and when one-fourth of this was injected into a previously standardized rabbit, the blood sugar fell from 0 121 to the definite hypoglycemia of 0 047

The Histogenesis of Renal Casts By HENRY JACKSON, JR , Boston, Mass

From observations on animals and man it would appear that some, at least, of the renal casts are formed by a degeneration and coalescence of the circular reticulum of the kidney This circular reticulum, in turn, is undoubtedly formed by a process of budding in the renal cells The cells of the convoluted tubules swell at their tip, form buds and these buds, becoming globular in shape, are pinched off from the parent cell and come to lie free in the lumen of the tubule

The process, at least in its initial stages, is to be regarded as a type of reaction to injury, rather than a process peculiar to the kidney, for similar if not identical changes have been found in other organs, especially the uterus and adrenal

The Mechanism of Phlorhizin Diabetes By HENRY B RICHARDSON and (by invitation) EPHRAIM SHORR, New York City, N Y

The nature of the action of phlorhizin is at present controversial Recent investigations have led a number of workers to the conception that the drug causes a break in the chain of carbohydrate oxidation, in other words a true tissue diabetes and not merely an increase in the permeability of the kidney

We have investigated the oxidation of carbohydrate in excised surviving tissue of the phlorhizinized rat, using the method developed by Warburg for the study of respiratory exchange in vitro With this technique it is possible to measure two quotients at the same time using the same organ White rats were phlorhizinized and when chemical and respiratory studies demonstrated that the action

of the drug was maximal, the kidneys or testes were removed for study Oxidation of carbohydrate was inferred when the respiratory quotient or the oxygen consumption was higher when glucose was added to the tissues than in its absence A control series of observations with normal animals has already been reported from this laboratory

In completely phlorhizinized animals the excised tissue was found to oxidize carbohydrate to the same extent as that of the normal animals Moreover when phlorhizin was added directly to the excised tissues of normal animals quotients of 0 800 to 0 930 were measured indicating that carbohydrate is oxidized in abundance Work is now being extended to the tissues of depancreatized animals Should these fail to oxidize carbohydrate, the inference will be that in the white rat at least phlorhizin has no effect on the combustion of sugar in excised tissue This would support the older theory that phlorhizin acts by increasing the permeability of the kidney

A Comparison of Glycolysis in Muscle and in Cancer Tissue By DAVID P BARR and (by invitation) ETHEL RONZONI, St Louis, Mo

It has been demonstrated by Warburg that malignant tumors possess a power of glycolysis much greater than that of normal tissue a property which may possibly furnish the energy for their rapid and continuous growth Superficially the process appears the same as the glycolysis which provides the energy for muscular contraction inasmuch as carbohydrate is converted in each instance to the same end product, lactic acid A more thorough examination, however, reveals important differences both in the carbohydrates which are utilizable and in the circumstances which modify the reactions. At the present time therefore, it is impossible to predict whether a substance which affects the glycolysis of muscle will similarly influence the glycolytic activity of tumor tissue

In 1923 Foster was able to prepare from the pancreas an alcoholic extract which would inhibit the glycolysis of muscle about 50 per cent In our experiments Foster s extract was tested for its effect upon the glycolysis of muscle, of muscle extract and of malignant tumors Foster's original statements have been confirmed It has been determined moreover that the pancreatic inhibitor will check almost completely the glycolysis which is produced by Meyerhof's recently described muscle extract While sufficient data has not been accumulated to allow a positive statement it appears that the glycolysis of malignant tumors is also inhibited by the pancreatic substance, although to a degree somewhat less than that observed in muscle and in muscle extract

On the Nature of the Immature Cells in the Blood in Leukemia By RAPHAEL ISAACS and (by invitation) GENEVA A DALAND Boston, Mass

Determination of the oxygen absorption by whole blood were made over periods of from one to seven hours in a specially devised microspirometer Comparative studies of the amount of oxygen used by blood from normal individuals and from

patients with chronic myelogenous leukemia show that the rate is faster when the leucocyte count is high than when the count is low The rate is not influenced markedly by the number of red blood corpuscles or the amount of hemoglobin, provided that the blood is saturated with oxygen when the observations are begun In terms of rate per 1000 cells, the adult polymorphonuclear neutrophiles use more oxygen per hour than the immature blood cells in chronic myelogenous leukemia, the most immature cells using the least In this respect the blood cells in leukemia behave in a way similar to that described by Warburg for cancer cells

The Effect of Liver Feeding on the Blood Sugar By WILLIAM P MURPHY and (by invitation) HARRY BLOTNER, Boston, Mass

We have noticed that persons partaking of a diet rich in liver often develop excessive hunger and complain of a group of symptoms similar to those described during the hypoglycemia resulting from insulin overdosage

This observation led us to make blood sugar curves in a series of cases following the ingestion of a known quantity of liver or fraction thereof The blood-sugar levels obtained following a test meal containing a known quantity of liver, fell and remained at a lower level than curves obtained after a meal containing similar amounts of protein, carbohydrate, fat and calories but from which liver was omitted In certain cases a marked lowering of the blood sugar level occurred such as is obtained following the injection of insulin The feeding of the fractions of liver composed of the connective tissue, insoluble fats and the liver proteins precipitated at pH = 5 resulted in a blood sugar curve similar to the ones obtained after feeding whole liver Certain other liver fractions effective in the treatment of pernicious anemia appear to contain an inappreciable amount of the blood sugar reducing fraction These observations suggest that liver may contain a blood-sugar reducing substance, active when ingested by mouth, non-toxic, and with an effect on blood-sugar concentration like that obtained with insulin

Demonstrable Differences between Antibodies in Natural and Artificial Hypersensitiveness By ROBERT A COOKE and (by invitation) W C SPAIN, New York City, N Y

There is considerable doubt regarding the relation of or the identity of the natural form of hypersensitiveness as manifested clinically in man by asthma and hay fever, and that form of hypersensitiveness immunologically induced in animal and man and generally called anaphylaxis

The problem is one of more than academic interest as a knowledge of the nature of the reaction may lead to a proper conception of the etiology and the prophylaxis of allergy in man

Comparative studies have been made on the reacting antibodies in the sera of (1) Naturally sensitized humans with asthma, (2) artificially sensitized (*a*) humans with serum disease, (*b*) rabbits

The sera have been tested for (1) The capacity to sensitize passively normal human skin areas, (2) the presence of specific precipitating antibodies, (3) the capacity to sensitize guinea pigs passively (the Dale reaction)

These studies have shown that both the artificially sensitized (anaphylactic) serum as well as the naturally sensitized (allergic) serum has the power passively to sensitize the skin of normal humans However, precipitating antibodies have not been found in naturally sensitive patients with asthma in striking contrast to their almost uniform presence in sensitized animals and their frequent occurrence in man after serum disease

By the Dale reaction it is shown that the naturally sensitive human serum will not sensitize passively a guinea pig's uterus, whereas the serum of an artificially sensitized man (serum disease) or rabbit has this ability

Studies on the Pathogenicity of Brucella Abortus Preliminary Report By ERNEST C DICKSON San Francisco, Calif

The question of the pathogenicity of Brucella abortus for human beings is one which is attracting considerable attention and is of importance because of the prevalence of infectious abortion in dairy herds in many parts of the country

Evidence of human infection is two-fold in character (*a*) Demonstration of living Br abortus in blood cultures and in urine cultures from patients suffering with low grade undulant fever, and (*b*) demonstration of specific immune bodies, particularly agglutinins, in the blood of patients who have low grade fever or in persons who are afebrile and who show no clinical signs of infection

If we accept the present methods for differentiating Br abortus from the true Br mellitensis there can be no doubt as to infection in the first group, but there is doubt in the minds of some investigators as to whether the presence of agglutinins in the blood of afebrile individuals is indication of active immunization from low grade infection or whether it indicates passive immunization produced by absorption of the agglutinins from the milk of infected cattle

Preliminary experiments on guinea pigs indicate that agglutinins are not found in the blood after feeding milk containing agglutinins but that they are found after feeding milk containing living Br abortus The agglutinin-containing milk was prepared by heating fresh milk to destroy all bacteria and adding immune goat serum of high agglutinin titre which had been prepared by immunizing a goat with killed antigen

In every instance in which agglutinins were demonstrated in the blood necropsy showed anatomical signs of abortus infection

Two Ward Infections of Rheumatic Fever By ERNST P BOAS and (by invitation SIDNEY P SCHWARTZ, New York City, N Y

Two ward infections of rheumatic fever have been observed at Montefiore Hospital In one instance five children developed rheumatic fever within a period of five weeks in another instance six children were taken ill within a period of

four weeks The rheumatic manifestations noted in these epidemics include pericarditis, heart block, arthritis, carditis One child in each epidemic came to autopsy and showed Aschoff bodies in the myocardium Only children with previous rheumatic heart disease contracted rheumatic infections, the non-rheumatic children in the same ward did not become ill It remains a question whether these were epidemics of true rheumatic fever or whether a non-specific infection activated the rheumatic virus latent in the several victims There is much evidence in the literature supporting the view that rheumatic fever may partake of the nature of an epidemic disease and that contact infection is possible

In a number of the cases of this series the bout of rheumatic fever was ushered in by a bronchopneumonia, and in these children it was impossible to know when the bronchopneumonia ceased and when the rheumatism began The two conditions merged insensibly one into the other We have been impressed with the importance of the lungs as a source of reactivation or as a possible portal of entry of rheumatic infection

The Antagonism of Cations in Their Action on the Living Cell By PAUL REZNIKOFF and (by invitation) ROBERT CHAMBERS, New York City, N Y

The mechanism of antagonism underlies all questions of immunity, therapeutics and the maintenance of physiological states To study the nature of antagonism in the living cell the Chamber's micrurgical technique was used By this method NaCl, KCl, LiCl, $CaCl_2$, and $MgCl_2$ and mixtures of these salts, were brought into direct contact with the interior of a living cell by means of injection as well as with the plasma membrane from the outside by immersion The cell used in the experiments was the Amoeba dubia which is relatively independent of osmotic changes

The results of these experiments indicate that antagonism depends upon the ability of the protecting agent to prevent the toxic agent from reaching or irreversibly affecting the vulnerable part of the cell The particular mechanism involved varies with the specific salts used and with the special part of the cell studied

Relationships between the Concentration of Sugar and Other Diffusible Substances in the Blood and the Rates of Their Supply, Circulation, Excretion, etc By R T WOODYATT, Chicago, Ill

Normal resting dogs given lactose intravenously at constant rates of 5 and 10 grams per 10 kilos per hour for 4 hours in half molecular solution show a rising lactose excretion in the urine in the first and second hours of each period and a virtually constant output thereafter, when the output per hour in the urine equals the intake showing that lactose is virtually insusceptible of chemical change in the body and insusceptible of excretion by channels other than the kidneys Other things being equal, the rate of lactose excretion depends on the rate at which lactose enters the circulating blood The failure of lactose to appear in the urine quantitatively at the rate of injection in the early hours of injection is due to the

progressive *retention* of unchanged lactose in the body until the total quantity rises to a certain level If S is the rate of lactose supply from all sources (in this case the rate of injection), E the rate of lactose excretion, R the rate at which the total quantity of lactose in the body increases, then, in the hours of equilibrium R is 0 and $S = E$ whereas, in the earlier hours, R has a positive value and $S = E + R$ In hours of equilibrium E is directly proportional to the total quantity of lactose in the body Q This quantity Q is contained in a state of aqueous solution in a certain volume of water in the body which is in the state that permits it to act as a solvent for lactose Anatomically this volume of water is represented by the blood, the lymph and analogous tissue fluids (blood plasma lymph phase) The lactose contained in the body tends to be in equilibrium throughout this phase being partitioned between the different anatomical parts in proportion to their relative volumes The *concentration* of lactose in the body as a whole, or in the watery phase of the body, or in any part of this phase such as the blood, need not be directly proportional to Q because the volume of the body as a whole, or of the phase in question, or of that part of the phase represented by the blood is subject to change with variations of the total volume of water in the body, in the phase in question, or in any part of this phase With Q constant, any change in the volume of the watery phase of the body necessitates a change of the blood lactose concentration, whether the volume of the circulating blood itself changes or not Whereas during life changes in the volume of blood in actual circulation may be relatively small, changes in the volume of the watery phase as a whole can be relatively great. Hence the possibility of constancy of S, and Q with wide variations of the blood lactose concentration or of constancy of the blood lactose percentage with S and Q varying or of S and Q constant and E varying by virtue of a shifting of water from the blood into the extravascular parts of the watery phase of the body or *vice versa* in response to physico-chemical factors

The rate of excretion of lactose depends primarily on the rate at which lactose enters the kidneys in the blood of the renal arteries The latter rate is expressible as the blood lactose concentration times the rate of blood volume flow through the renal arteries

Physico-Chemical Changes in the Blood of a Case of Pernicious Anemia By A V Bock and (by invitation) D B Dill, C Van Caulert and H Folling, Boston, Mass

The Effects of Anesthetics on the Recovery Process of Skeletal Muscle By J C Meakins and (by invitation) C N H Long, Montreal, Canada

According to A. V Hill, Meyerhoff and Embden, during muscular contraction glycogen is broken down to lactic acid via the intermediary substance "lactacidogen," while during recovery four fifths to five sixths of this lactic acid is reconverted into glycogen by both the active and passive muscles and also by the

liver During an investigation on the relative parts played by the muscles and liver in this synthesis it was found

1 That anesthetics (amytal, ether and chloroform) prevent this resynthesis to such a marked extent that three hours after stimulation under amytal practically none of the glycogen broken down had been restored

2 Under amytal this resynthesis is delayed as long as the effect of the anesthesia persists, i e , up to 12 hours, but under the volatile anesthetics it commences as soon as the full effect of them has worn off

3 Under *local* anaesthesia an 80 to 100 per cent resynthesis of the glycogen broken down had occurred within three hours after stimulation

4 Insulin by promoting glycogen deposits throughout the body hastens this recovery process, even when anesthesia is present

5 Infusions of glucose without insulin act in the same manner

6 The effect of anesthetics alone without any stimulation is to cause a decrease, some 10 to 15 per cent in 3 hours, in the glycogen content of the muscles

The Source of Readily Available Body Calcium By WALTER BAUER and FULLER ALBRIGHT (by invitation) and J C AUB, Boston, Mass

Collip's parathyroid extract raises the blood calcium and the calcium excretion However, no one has ever demonstrated whether this calcium comes equally from all bone structure or from some particular portion of each bone It has been proven in lead poisoning (1), that upon administration of parathormone the excretion of both lead and calcium is increased at first, but after replacing the calcium loss by a high calcium diet a second administration of parathormone increases the calcium excretion alone This indicates that a certain supply of calcium is readily available for sudden demands The anatomic structure and blood supply of the bone trabeculae suggests these structures as the most probable source of this calcium

Our problem was to see if we could influence the amount of cancellous bone by long continued administration of parathormone and by high and low calcium diets Long continued administration of parathormone to rabbits resulted in definite signs of decalcification, most marked at the epiphyseal portion, easily demonstrated by x-ray These bones on cross section, when compared with those from their normal litter mates showed a marked reduction in the number of trabeculae

Eight cats were chosen for the experiment upon effect of diet Four were placed on a low calcium diet of liver and meat and four on a high calcium diet of milk At the end of six months the left foreleg was amputated at the shoulder and the diets reversed At the end of a like period of time the animals were sacrificed The bones representing the period when the cats were on a high calcium diet constantly showed many more trabeculae than did the bones representing the low calcium diet period

In conclusion we can state the following

1 The cancellous bone serves as the most readily available supply of calcium

2 One can decalcify bones by the long continued administration of parathormone

3 The decreasing potency of Collip s parathyroid extract seen in certain cases after prolonged administration may be dependent upon the depletion of this easily available calcium

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The Influence of Pituitrin and Adrenalin on Insulin By REGINALD FITZ and (by invitation) HARRY BLOTNER, Boston Mass

We have observed in normal rabbits the effect on the blood sugar concentration of varying doses of insulin, pituitrin and adrenalin Blood sugar curves obtained following the intravenous injection of insulin were much alike regardless of the amount introduced There was, uniformly, a fall in blood sugar concentration followed by a more or less rapid rise to normal

Pituitrin acted in an opposite fashion to insulin Following its injection there was at first hyperglycemia followed by a fall in the blood sugar concentration with a resulting blood sugar curve almost directly the rever e of that obtained with insulin In one fatal case the blood drawn immediately after death contained so low a sugar concentration as to suggest insulin poisoning

Adrenalin acted not so exactly in an opposite fashion to insulin Following its injection, there was at first hyperglycemia followed by a fall in the blood sugar concentration The fall in the blood sugar level, however, was not immediate and resembled that obtained after intravenous injection of glucose rather than that obtained after pituitrin and was not directly the reverse of that obtained with insulin In one fatal case of adrenalin poisoning the animal died with a very low blood sugar level and in convulsions The clinical appearance suggested insulin poisoning

We attempted to ascertain whether the fall in blood sugar concentration and resultant hypoglycemia obtained after injections of pituitrin and adrenalin were of the same nature due to insulin set free in antagonism to the hyperglycemia at first produced by these substances or due to some other mechanism Normal blood was transfused into an animal It was followed by a pronounced hyperglycemia which gradually disappeared Blood drawn from an animal which had been injected with 5 units of insulin 15 minutes previously was transfused into a normal rabbit. There was no resultant hyperglycemia, in contrast to that observed in the control animal, but an initial hypoglycemia and gradual rise to the normal level so that the curve obtained was entirely comparable to that seen in animals treated with insulin alone Blood drawn from an animal which had been made hypoglycemic from pituitrin was transfused into a normal rabbit There was no resultant hyperglycemia, in contrast to that observed in the control animal, but there was an initial hypoglycemia and gradual rise to the normal level so that the

curve obtained was entirely comparable to that seen in animals treated with insulin alone and to that recorded in the animal transfused with "insulinized" blood Similar transfusion experiments were carried out by injecting normal animals with blood made hypoglycemic from adrenalin and glucose In these cases there was an initial hyperglycemia followed by a return to the normal level so that the resultant curves resembled more closely those obtained in the control experiments than those obtained from "insulinized" or "pituitrinized" blood

These experiments suggest that the effect of pituitrin upon the blood sugar is directly antagonistic to that of insulin, and that pituitrin hyperglycemia is controlled by a compensatory increase in the circulating insulin In contrast, the disappearance of an excessive amount of blood sugar obtained from adrenalin injections appears to take place through some other mechanism and without the aid of an appreciable increase in the circulating insulin

The Clinical Applications of Quantitative Pettenkofer Tests to the Blood By L G Rowntree and (by invitation) M Aldrich and C H Green, Rochester, Minn

Abnormal Specific Dynamic Action of Protein, Glucose and Fat Associated with Undernutrition By Edward H Mason, Montreal, Canada

Six cases of undernutrition with definite abnormalities of specific dynamic action for protein, glucose and fat are reported In five the onset of undernutrition was associated with definite symptoms of ill-health, the loss of weight varying from 5 to 28 kilos These five cases had low basal metabolic rates

The findings were controlled by similar experiments in seven normal individuals

In four of the cases the maximum percentage increase in heat production over the basal level after a fat breakfast containing 74 grams of fat varied from 20 7 to 47 7 per cent In three cases, after 100 grams of glucose the maximum rise in heat production varied from 22 8 to 52 0 per cent Five cases, after a meal containing 150 or 200 grams of beef, showed a more rapid percentage rise in heat production than did the controls, but the total caloric increase did not vary greatly from the controls

Regulation of the food intake in accordance with the altered specific dynamic action has resulted in a gain of weight in four cases In the other two the period of observation has been too brief to judge

Coincident with an improvement of nutrition the altered specific dynamic action returned to normal (two cases studied)

Varicella in Monkeys Nuclear Inclusions Produced by Varicella Virus in the Testicles of Monkeys By T M Rivers, New York City, N Y

Many workers believe that acidophilic nuclear inclusions are the manifestation of the presence of certain viruses, amongst which is varicella In a previous communication a report was made concerning eosin-staining nuclear inclusions

observed in the cells of monkeys' testicles inoculated with emulsified human varicella papules and vesicles At the time of the previous paper there were reasons for the belief that the nuclear inclusions were produced by the action of varicella virus Proof of this however, was obtained only recently by means of neutralization and reinoculation tests and consists, in brief of the following facts Nuclear inclusions were not found in monkeys' testicles inoculated with a mixture of varicella virus and convalescent varicella serum On the other hand, they were found in testicles inoculated with a mixture of virus and non immune serum collected from varicella patients early in the disease Furthermore, the inoculation of one testicle with varicella virus prevented the formation of nuclear inclusions in the other one when it was inoculated at a later date with the same virus

Insulin Utilization in Acidosis By H FIELD, JR. (by invitation) and L H NEWBURGH, Ann Arbor, Mich

An attempt has been made to determine the factors involved in the increased dosage of insulin required to produce a given effect on the sugar metabolism during the state of acidosis.

Observations have been made on completely depancreatized dogs receiving a constant intravenous infusion of glucose and insulin by means of a motor-driven pump It has been possible to adjust the dosage of insulin and glucose so that the blood sugar, reduced to a normal level by a previous dose of insulin, has been maintained at that level In animals so treated, the intravenous injection of hydrochloric acid has been followed by a sharp rise in blood sugar In other experiments the order of procedure was reversed and acid injected at the beginning In such animals it has been necessary to use a smaller inflow of glucose to maintain a constant blood sugar The subsequent injection of a neutralizing dose of sodium bicarbonate has been followed by a progressive decrease in blood sugar

Since, by such treatment the distribution of ions has been changed but none of foreign character added, this is considered to be evidence of a depressing influence on sugar metabolism of increased H ion concentration

The Specific Treatment of Pneumococcus Type II Pneumonia By HORACE S BALDWIN and WHEELAN DWIGHT SUTLIFF (by invitation) and RUSSELL L CECIL, New York City, N Y

Pneumococcus Type II pneumonia is the most serious type encountered in Bellevue Hospital In 89 cases that received no specific therapy the death rate was 42 6 per cent Type II pneumonia is the pneumonia of septicemia In a series of cases studied with blood cultures 43.3 per cent showed septicemia, and of the septic cases 90.3 per cent died On the other hand when the blood culture remained sterile the death rate was only 16 per cent The object of the present study was to determine whether any of the specific agents now available for the treatment of Type II pneumonia were capable of sterilizing a patient's blood and

producing a balance of immune bodies in the patient's serum Some of these cases were treated with a potent Type II antipneumococcus serum, others were treated with a concentrated serum prepared by the method of Felton

Conclusions With a potent Type II antipneumococcus serum it is possible to sterilize the blood in a certain number of cases of Type II pneumonia The most striking results are obtained when serum is administered early in the course of the disease

The Inhibiting Influence of Formaldehyde upon the Dale Reaction By ARTHUR I KENDALL (by invitation) and HARRY L ALEXANDER, St Louis, Mo

Kendall (1) recently has shown that formaldehyde will inhibit smooth muscle contraction induced by histamine It is believed that formaldehyde acts upon the amine group of histamine and that H_2 is removed The resulting product is a methylene compound similar to that obtained in formol titration

Essentially nothing is known concerning the stimulus which causes smooth muscle to contract in anaphylaxis The above principle was applied to the Dale experiment as follows The two uterine horns of a guinea pig sensitized to egg-white were suspended each in a separate Dale apparatus with baths of 150 cc of oxygenated Tyrode's solution To one bath 0 5 cc egg-white solution was added and the immediate characteristic smooth muscle contraction recorded To the other bath treated with 1 0 cc of 3 per cent formaldehyde solution, 0 5 cc egg-white solution was added No contraction resulted This bath was washed out and refilled with fresh Tyrode's solution The addition of histamine then caused muscle contraction indicating that the contractility of muscle had not been impaired by formaldehyde

When smooth muscle was allowed to contract in the absence of formaldehyde the reaction could be inhibited immediately by formaldehyde This phase as well as the nature of the reaction is being studied

It is possible that this demonstration may indicate the nature of the stimulus of smooth muscle contraction in anaphylaxis

Bibliography (1) Proc Soc Exp Biol and Med , 1927, xiv, 316

Development of Agglutinins and Protective Antibodies in Rabbits Following Inhalation of Pneumococci By E G STILLMAN, New York City, N Y

Rabbits are very susceptible to infection by inhalation of Type I pneumococci When rabbits are exposed to a pneumococcus spray, the bacteria readily penetrate into the lower respiratory tract The pneumococci which reach the periphery of the lungs as a result of this procedure usually disappear within a few hours but a generalized and fatal septicemia frequently appears later Pneumococci may then be recovered from the periphery of the kidney, liver, and spleen In the animals which die, pleurisy and pericarditis are common but pneumonia does not occur

Rabbits may recover from pneumococcus septicemia

Following repeated inhalations of Type I pneumococci agglutinins remain stationary after the fifth exposure, but the percentage of rabbits showing protective antibodies in their sera steadily rises

The Heart after Severe Diphtheria By T D JONES (by invitation) Charlottesville Va, and PAUL D WHITE, Boston, Mass

The aspect most important for study in dealing with cardiovascular disease is its etiology, since further progress in the control and prevention of such disease is dependent on greater knowledge of its causes One of the infections which is known sometimes to involve the heart severely during its course is diphtheria, but there has been insufficient knowledge of the more remote effects of diphtheria on the heart Hence a study has been made by us by history, physical examination and electrocardiograph, of 100 young people who had severe diphtheria a few years before the examination, without complications from congenital defects or rheumatic valvular lesions From this study there is no evidence of appreciable chronic effects of diphtheria on the heart

Hyperthyroidism Associated with Bacterial Endocarditis By JOSEPH A CAPPS, Chicago, Ill

Skin Reactions to Streptococcus Filtrates in Acute Streptococcus Infections in Acute Nephritis By OSCAR C HANSEN PRUSS and D P O BRIEN (by invitation) and WARFIELD T LONGCOPE, Baltimore, Md

Skin reactions to filtrates of various strains of streptococci have been studied in normal people and in patients with acute nephritis, and in patients suffering from acute streptococcus infections such as tonsillitis

The organisms which were used for the production of the toxins were obtained from the tonsils (either by tonsillar swabs or from the interior of the infected organ after operation) or from the sinuses or adenoid tissue of individuals which showed evidences of an active infection Freshly isolated organisms were grown on blood agar slants for twenty four hours and then transferred to 7 4 bouillon where they were allowed to grow for eighteen hours The broth culture was then filtered through a Berkefeld N candle and the "toxin" injected intracutaneously in amounts of 0 1 cc. in dilutions varying from 1 100 to 1 5000 The reactions were read after eighteen and twenty four hours Reactions were interpreted as positive when the area of erythema, occasionally associated with edema, measured at least 1 cm in diameter As a control 7 4 bouillon was injected simultaneously in 1 100 dilution A Dick reaction was performed at the same time

1 Reactions were made in fifty five normal adults and twelve normal babies as controls Twenty per cent of the normal adults showed moderate reactions to at least one of the several different strains of streptococcus filtrates in dilutions of 1 100 These did not bear any relation to the presence or absence of a positive Dick test In 16 5 per cent of the cases reactions occurred in dilutions

greater than 1 100 (0 001 cc of toxin) The babies varied in age from two to seven days, none of them gave a positive skin reaction to the Dick toxin or to the various streptotoccus filtrates The mothers of these babies were tested simultaneously with streptococcus filtrate and Dick toxin and in several instances gave positive reactions to the Dick toxin, streptococcus filtrates, or both

2 Thirty-two adults suffering from acute tonsillitis or other forms of streptococcus infection were tested during the acute stage of the disease and at intervals after recovery Cultures from the throat, nose or sinuses were made each time that they were subjected to skin tests Positive skin reactions with 0 001 cc of toxin were obtained almost uniformly in the acute stage of the disease, 37 5 per cent reacted to dilutions greater than 1 100, few reacted to more than three or four strains It was found that this susceptibility to the streptococcus filtrates diminished as the infection subsided, or persisted if the organisms remained in the nose and throat for any length of time In several instances it was possible to test the individuals with toxins made from the organisms obtained from their own nose and throat, to which they often reacted more vigorously than to heterologous strains

3 Sixteen adults suffering from acute or subacute nephritis were tested repeatedly during the course of the disease Positive skin reactions were obtained in 80 per cent of these cases during a period in which the evidences of acute illness were at their height It was found, however, that these individuals tended to react to most of the strains which were tried Fifty-six per cent gave reactions in dilutions greater than 1 100 These positive reactions did not bear any relation to the presence or absence of positive Dick tests Most of these individuals were also tested with filtrates of streptococcus cultures from organisms obtained from their own nose, throat and sinuses It was found that they were likely to react more strongly to filtrates from their own strains than from heterologous strains, and that they remained susceptible to these filtrates for a longer time than they did to the various other filtrates, especially if the local infection persisted In a few instances a diminution, or even a complete loss of skin reaction to the streptococcus filtrates was observed when the acute nephritis subsided

The Effect of Intravenously Injected Phosphate Solutions on the Blood and Urine Phosphorus in Man By I Schulz (by invitation) and N M Keith, Rochester, Minn

The solution injected was a mixture of dibasic and monobasic sodium phosphates, balanced to give a pH of 7 1 to 7.2 Amounts up to 15 mgm of phosphorus per kilogram of body weight were administered No untoward subjective effects were noted The normal subject was kept on a weighed, controlled diet Phosphorus and calcium studies were made on blood, urine and feces

After injection of the phosphate solution, there occurred an immediate rise of inorganic phosphorus in the blood, followed by a rapid fall The normal phosphorus concentration was approached in four hours The urine output ran

parallel to the blood concentration An immediate rise of from 15 to 30 times the average normal output occurred, followed by a rapid drop for 3 hours The phosphorus in the feces also definitely increased The urinary excretion of calcium was slightly increased The calcium of the feces was not affected The ingestion of calcium chloride previous to injection of phosphate solution did not alter either the amount or the path of excretion of the phosphorus, although the calcium content of serum, urine, and feces was definitely increased

In cases of renal disease with retention of creatinine and with a low excretion of phenolsulphonephthalein, there was a retention of phosphorus after the injection of phosphate solution

Liver Fractions in Pernicious Anemia By RANDOLPH WEST, New York City, N Y

Since Minot's (1) demonstration of the great therapeutic efficacy of a high liver diet in pernicious anemia, we have been endeavoring to determine what substances in liver are responsible for this effect

Spermine phosphate (2) which is present in much greater concentration in liver, kidney and pancreas than in muscle tissue, was fed in doses of 100 to 150 mgm daily to four cases without any improvement in three of them over two-week periods On switching to liver the improvement was dramatic.

Thioneine recently isolated by Benedict (3) from red blood cells was fed to one patient with a negative result

Fresh minced moist liver was next extracted with 60 per cent alcohol (including tissue water), then ether, and finally boiling 95 per cent alcohol. The three extracts were filtered through paper and evaported to dryness in vacuo This residue in 10-gram doses twice daily was highly efficacious in five consecutive cases

The 60 per cent alcohol fraction alone, after evaporation to dryness and repeated washings with 95 per cent alcohol and ether was then found effective in 8- to 10-gram doses daily in one case

The material is water soluble, biuret negative, iron free, and contains 5 7 per cent N, 2 4 per cent amino-N, 2 per cent P and 1 per cent S

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Further Studies on the Relation of Monilia to Pernicious Anemia By O GARCIA CECILE GARCIA, and NANCY BOYCE (by invitation) and G O BROUN, St Louis Mo

Ten strains of Monilia derived from cases of pernicious anemia, are closely related morphologically to each other and to the Monilia Psilosis of Ashford Strains isolated from cases other than pernicious anemia sometimes show similar

morphological characters and sometimes differ widely from the Monilia Psilosis type

The pernicious anemia strains so far studied all produce acid in media containing dextrose, levulose, maltose, galactose, dextrin and sucrose The action on lactose, mannite, inulin and xylose varies with different strains They do not produce acid in arabinose, sorbitol, raffinose and dulcite Four pernicious anemia strains which produce acid in dextrose, levulose, maltose, galactose, dextrin and sucrose are identical in fermentation reactions with nine other strains isolated from a wide variety of pathological conditions One strain shows identical fermentation reactions with Monilia Psilosis of Ashford The others fall into two groups which differ from all other strains studied

The Monilia complement fixation test carried out with antigens made from a number of strains of Monilia show definite specific differences between strains The pernicious anemia strains show some serological relationships but also some serological differences

The Monilia isolated from pernicious anemia cases are therefore not absolutely identical although belonging to a closely related group

Observations on the Size of the Red Blood Corpuscles Before and After Splenectomy in Hemolytic Jaundice DUNCAN GRAHAM and (by invitation) R F FARQUHARSON and E J MALTBY, Toronto, Canada

In the investigation of cases of hemolytic jaundice, both familial and acquired considerable variation has been found in the degree of microcytosis present in the blood of different patients In some it was so slight as to be of no significant importance in the diagnosis of the disease A more careful study was therefore made of the size of the red blood corpuscles at different times, both before and after splenectomy, together with observations on the color volume, and icterus indices, and the resistance of the red blood corpuscles to hypotonic salt solution Measurements were made of the diameter of the red blood corpuscles at intervals before and after splenectomy in five cases of hemolytic jaundice and the frequency distributions of the red blood corpuscles of different sizes were determined

Summary of results 1 The mean diameter of the red blood corpuscles in cases of hemolytic jaundice before splenectomy is less than normal

2 Shortly after splenectomy the mean diameter of the red blood corpuscles remains less than normal and may be even less than before splenectomy

3 Later, after splenectomy, the mean diameter of the red blood corpuscles becomes greater and the percentage of cells having the mean diameter of normal red blood corpuscles increases

4 Both before and after splenectomy the mean diameter of the red blood corpuscles may show definite variations at different times, more marked in certain cases than others

5 The percentage of red blood corpuscles less than seven microns in diameter

decreases within a few weeks after splenectomy but this percentage always remains greater than normal.

6 The individual character of the microcytes present in cases of hemolytic jaundice, before and after splenectomy, remains the same

The significance of these results is discussed

Skeletal Changes in Gaucher's Splenomegaly By SARA WELT, and N ROSENTHAL (by invitation) and B S OPPENHEIMER, New York City, N Y

The diagnosis may be aided by finding (1) gross skeletal changes (gibbus, pathologic fracture, etc.), (2) characteristic x ray changes in the bones (3) Gaucher cells in material secured by bone-marrow puncture, splenic puncture, or splenectomy Gross osseous changes were first described by Pick (1922) and have been present in 2 of our 8 cases collected since 1918 Characteristic radiographic changes were found in 3 cases, and bone-marrow involvement also in 3 cases The family of every case of Gaucher disease should be investigated for gross skeletal changes, and should also be x rayed to detect evidence of the disease

Gaucher's original conception that this disease is a neoplasm of the spleen has been abandoned Since the Gaucher substance has now been demonstrated to contain "kerasin," one of the cerebrosides, and a large proportion of phosphatids, the disease should now be considered a disorder of lipoid metabolism in which complex lipoids fail of complete disintegration and are stored in the histiocytic elements of the reticulo-endothelial apparatus Splenectomy cannot cure the disease and is indicated only if the weight of the spleen becomes burdensome, or if the hemorrhagic tendency becomes serious The characteristic low blood platelet count returned to normal after splenectomy

The Effect of Emotion on the Basal Metabolic Rate By SOLOMON STROUSE and (by invitation) H. F BINSWANGER, and HARRY SEGAL, Chicago, Ill

It would seem that one of the easiest methods of determining the effect of emotion on the basal metabolic rate would be its study in hospital patients just before operation A series of such patients with various conditions, including toxic goiter were carefully studied before and after knowledge of the impending operation The basal metabolic rate, blood pressure, pulse rate and signs of disturbances of the nervous system were noted before the patient knew of the impending operation The night before the operation, the patient was told about the operation and determinations were again made the next morning just before going into the operating room Patients included in this study received no drugs The results indicated practically no effect from this type of emotion in any of the patients studied

Sulphemoglobinemia By WALTER R CAMPBELL and (by invitation) R F FARQUHARSON Toronto, Canada

Several cases of so-called enterogenous cyanosis with sulphemoglobin in the

red blood cells have been reported in the literature Three new cases are described Spectographs demonstrating the identity of the pigment in these cases with sulphemoglobin are shown New methods for the identification and estimation of the abnormal blood pigment have been devised Chemical and bacteriological studies have been undertaken on these patients The diagnosis, etiology and treatment of this condition are discussed

Observations on the Etiology of Chronic Myocarditis By JAMES P O'HARE, and (by invitation) ABNER W CALHOUN, and HUGO O ALTNOW, Boston, Mass

In May, 1922, Walker and one of us (O'Hare) presented to the Association of American Physicians a series of observations made on the relation between blood pressure and peripheral and retinal arteriosclerosis In that paper we concluded that the finding of retinal arteriosclerosis almost invariably indicated hypertension, present or past We now wish to present a series of cases of known chronic myocarditis without valve lesions and with normal blood pressures but with retinal arteriosclerosis These patients are known to have previously had hypertension These cases are offered as proof of the theory that chronic myocarditis without valvular or thyroid disease is part of a hypertensive syndrome We expect to have a group of cases of chronic myocarditis of valvular origin to contrast with this hypertensive group

Studies of the Heart in Thyroid Disease I Changes in the "T" Wave of the Human Electrocardiogram Following Iodin Medication and Thyroidectomy By WALTER W HAMBURGER and (by invitation) MORRIS W LEV, and HELEN C HOWARD, New York City, N Y

This paper is the first of a series of reports concerning the heart in thyroid disease Clinical studies of the pulse rate, blood pressure, and heart size during rest, digitalis and iodin medication, and after thyroidectomy, are in progress, as well as experimental studies on the production of iodin and thyroid myocarditis similar to the work of Takane and Hashimoto

The present paper concerns the changes in the "T" wave of the human electrocardiogram following iodin medication and thyroidectomy These changes, which are not always constant, may be stated in general as follows In those cases which are responding favorably, there is a marked lowering of the height of the "T" wave, in some cases continuing to inversion (negativity) In those cases, not responding favorably, the "T" wave increases in height Similar, though less marked changes occur in some cases in the "P" wave These changes are probably not specific iodin effects, but more likely indicate changes in the effectiveness of the heart muscle, similar to the changes in the "T" wave resulting from digitalization Evidence is also offered of the possibility of these changes being due to variations in sympathetic (accelerator) tone, in accord with the experiments of Rothberger and Winterberg

It is hoped that further studies will show that these changes may serve as a guide for iodin tolerance and sufficient dosage, as well as an aid among the differential indications for digitalis or iodin in the treatment of the goitre heart

Cardiac Pain with Paroxysmal Tachycardia By ARLIE R BARNES (by invitation) and FREDERICK A WILLIUS, Rochester, Minn

Nineteen cases of paroxysmal tachycardia are cited to call attention to the fact that pain, which simulates closely that seen in angina pectoris, may be present in the attacks The electrocardiographic findings are discussed A comparison of the duration of time since the first seizures occurred and the time elapsing since pain first occurred in the seizures is made A detailed description of the type, location, and radiation of the pain together with attendant phenomena is given The factors precipitating the pain and bringing about its relief are contrasted with those acting in angina pectoris Abstracts of the histories and findings in six patients are included Prognosis is discussed and the favorable outlook in these patients as contrasted with patients suffering with angina pectoris is pointed out Attention is called to the fact that favorable results from therapy may be expected only when the treatment is directed toward the control of the paroxysms of tachycardia Finally, the mechanism probably concerned in the production of pain in these patients is discussed in the light of recent physiological experiments on coronary blood flow and on the circulation in attacks of paroxysmal tachycardia.

Ergotamine in Hyperthyroidism By E COWLES ANDRUS, Baltimore, Md

Ergotamine tartrate injected intravenously in dogs after the vagus has been functionally excluded slows the rate of the sinus rhythm, depresses A V conduction and delays the transmission of the excitatory process in the auricle.

Clinical use of this drug has been made in cases of hyperthyroidism Administered in doses of from 3 to 6 mgm per diem before and after operation ergotamine inhibits the post-operative tachycardia and enhances the rate of recovery from operation

The Relation of Size of the Heart to Effectiveness of Digitalis Therapy By A E COHN, H. J STEWART, and (by invitation) A. R GILCHRIST, New York City, N Y

Harrison and Leonard contend that digitalis decreases cardiac volume output and rate of blood flow This idea modifies current notions so much that we have tested its validity We conclude that heart size neglected by them is of prime importance If digitalis reduces this below a certain volume, output and flow necessarily decrease. In disease, increased cardiac size is similarly reduced We studied blood flow in normal dogs' hearts during normal rhythm and auricular fibrillation with and without digitalis In artificial fibrillation cardiac size increased and the rate of flow decreased When digitalis was given both size and

flow returned towards normal After cessation of fibrillation but with digitalis there was a further return towards normal and *beyond*, so that blood flow was reduced This last state corresponds with Harrison and Leonard's result

The result with digitalis therefore in normal regular hearts differs from that in enlarged fibrillatory ones and, by inference, from that in enlarged regular ones The size of the heart should have been considered by Harrison and Leonard, their inferences without considering this factor are not justified Current belief is therefore correct

Observations on Synovial Fluid By RALPH PEMBERTON and (by invitation) F A CAJORI, Philadelphia, Pa

The concentration of certain diffusible constituents and the reaction are very similar in blood and synovial fluid It has also been shown that glucose readily diffuses from the blood into synovial fluid

In the present experiments synovial fluid and blood have been compared with respect to non-protein nitrogen, urea and amino-acids Almost identical values have been found

The proteins of synovial fluid, which are present in lower concentration than in plasma, have been fractionated The globulin content was found to vary more in different synovial fluids than is the case in plasmas and the albumin-globulin ratio is somewhat higher than is usually encountered in plasma This was particularly true in the synovial fluid of the one case of anasarca studied The mucin content gives to synovial fluid its high viscosity

One sterile synovial fluid with a white cell count of 14,000, pH 6 50, and containing only traces of sugar was studied It was found that rapid glycolysis occurred in this fluid with the production of lactic acid The high acidity and absence of sugar, characteristic of "septic" joint fluids, are probably to be ascribed to glycolysis by the leucocytes occurring in the joint cavity The degree of acidity and the amount of sugar may be a measure of the extent of the inflammatory process

The Clinical Symptoms of Bilateral Thrombosis of the Suprarenal Veins By EDWIN F HIRSCH and JOSEPH A CAPPS, Chicago, Ill

A man, 30 years of age, came under observation because of weakness, shortness of breath, nervousness, sleeplessness, fulness of the head and headache, poor appetite, and attacks of cyanosis accompanied by unconsciousness The attacks of cyanosis increased in severity, and death occurred nineteen days after admission to the hospital and about six weeks after the onset of symptoms A careful post-mortem examination of the head, neck, and trunk demonstrated a bilateral thrombosis of the suprarenal veins, and no other lesions that could be considered sufficient to cause death The thrombi, histologically, were mixed, containing both recent portions and older portions in the process of organization The origin is considered to be probably bacterial Our interpretation of the

clinical symptoms is that they followed temporary sudden suppression of the function of the suprarenal glands recurring until finally death occurred

Some Experimental Observations on the Effect of Diathermy on the Circulation By C L Brown and H L Alt (by invitation), and S A Levine, Boston, Mass.

Experiments were carried out on rabbits to study the effect of diathermy on the heart size, electrocardiographic changes and the blood pressure It was first necessary to study the temperature changes inside the body when the diathermy electrodes were applied on the outside of the chest It has generally been assumed that the temperature is greatest mid way between the electrodes, and that in that way localized heat could be produced within the body In our experiments we found that temperature inside the chest is a great deal less than the skin temperature In fact, in order to obtain great increases in temperature in the vicinity of the heart, it was necessary to raise the temperature of the skin so that burns and sloughs were produced One reason for this is that any heat produced in the vicinity of the heart would be carried off by the blood stream There is also reason to believe that the rise in temperature within the body when diathermy is used clinically is very slight With the method we employed, no appreciable change in the size of the heart by x ray examinations and no significant electrocardiographic changes resulted but a temporary slight fall in pressure was obtained as a result of diathermy

A Critical Study of Diathermy By Carl A L Binger and (by invitation) Ronald V Christie New York City N Y

The Static System and Its Relation to Cerebellar Function By J Ramsay Hunt, New York City N Y

According to the author the function of motility is subserved by two separate systems which are represented at all physiological levels of the central nervous system.

The Kinetic System is concerned with movement and the Static System with posture The *Kinetic* System is responsible for fibrillary twitchings, the tendon reflexes convulsions, chorea tremor and other forms of motional disturbance The *Static* System is responsible for the "lengthening and shortening" reactions of muscles, myotonia catatonia and cerebellar symptoms The cerebellum is the chief ganglion of the Static System and with its cerebral and spinal connections constitutes the Static System The various components of the cerebellar syndrome —asynergia—are all referable to a disorder of posture—synergy *Posture—synergy* therefore, is the essential function of the cerebellum

The Treatment of Pernicious Anemia with a Vitamin Rich High-Caloric Diet By Karl K Koessler and Siegfried Maurer (by invitation) Chicago Ill

The vitamin theory of pernicious anemia which forms the basis of the dietetic treatment in man and of the experimental production of the blood picture in the animal may be briefly expressed as follows

1 The blood changes and the changes in the gastro-intestinal tract may be due to underfeeding with vitamin A or to a vitamin A imbalance over a long period of years

2 The nervous symptoms may be related to a deficiency in vitamin B

3 The tendency to hemorrhages may be due to a partial or complete lack of vitamin C

Twenty-five patients with pernicious anemia have taken a diet devised to be rich in vitamins A, B and C, and of high caloric value from three months to nearly two years

From two to three weeks after the diet has been started a prompt remission sets in Blood regeneration increases and proceeds in a normal manner Blood destruction ceases and inside of from ten to fourteen weeks the blood is normal in every respect numerically as well as morphologically One patient died suddenly two months after treatment had been instituted No autopsy was obtained All others are alive and much improved subjectively as well as objectively No relapse has occurred in any one of the patients since the treatment has been started None of our patients has received a blood transfusion Associated with the improvement of the blood is frequently a definite improvement in the subjective and objective symptoms due to spinal cord degeneration The achylia gastrica has remained unaffected by the treatment

A METHOD FOR THE DEMONSTRATION OF CALIBRE CHANGES IN THE BRONCHI IN NORMAL RESPIRATION

By PETER HEINBECKER[1]

(From the Department of Physiology Washington University School of Medicine, St Louis Missouri)

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Article by Blumgart and Weiss

Page 425 Reference 15 should read Hewlett, C W, General Electric Review, August, 1927

(Forestier, 1926) It was [illegible] sibility of using this substance to demonstrate any changes in the size of the bronchi which might occur during normal respiration

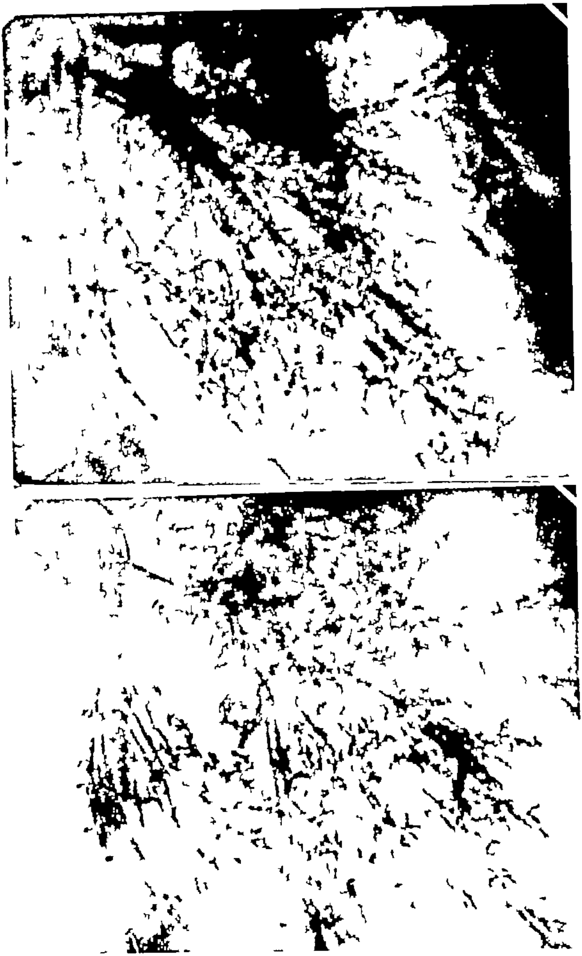
For the observations on living subjects, one cat, two dogs, and five human subjects were employed The animals were anesthetized with urethane and the oil administered by tracheal puncture In man the films were taken in the course of diagnostic procedures No anesthetic was required, the technique described by Singer (1926) being employed After injection of the oil, x-ray films were taken in man during the actual process of breathing and also while holding the breath at the end of inspiration and at the end of expiration

[1] Fellow in Medicine of the National Research Council

The respiratory movements were recorded by a pneumograph held around the chest by a tape and attached to a tambour The moment of the time of exposure of the film was signalled on the record To record accurately the time of exposure with reference to the particular phase of respiration it is well to have the kymographic marking key and the x-ray circuit operated by the same switch, but it was not possible to arrange this in these experiments All radiographs were taken at a constant distance, three feet, and the exposures made very short to avoid motion in the pictures

RESULTS

Figure 1 shows a set of radiographs taken with man as the subject, the breath being held, at the end of full inspiration (film no 1) and at the end of full expiration (film no 2) Figure 2 was obtained also in man but with the chest in motion, the exposures being made at a time near the end of normal inspiration (film no 1) and at a time near the end of normal expiration (film no 2) Examination of figure 1 indicates at once that there is a demonstrable change in the calibre of the bronchi during full respiratory movements The bronchi and bronchioles are largest at the end of full inspiration and smallest at the end of full expiration Figure 2 shows slight, if any, change in the calibre of the bronchi This is the normal finding in quiet respiratory movements except as shown in figure 3 The latter taken also in man shows an interesting feature when examined in connection with figure 4 to indicate the time of the exposures In some of the long bronchi, particularly in those to the lower lobe, there is an actual narrowing during inspiration (fig 3, no 1) when compared with the film taken during expiration (fig 3, no 2) even though the latter film is taken somewhat later in expiration than the first film is in inspiration While these findings were puzzling at first, it was seen that they could be explained on the basis of passive changes Our radiographs showed the bronchi, especially the larger ones to the lower lobe, lengthened considerably during inspiration Ballon and Ballon (1927) have given an excellent description of the changes in position and length occurring in the bronchi during respiration Passive mechanical changes in calibre must be the resultant of linear and radial traction The linear changes would be



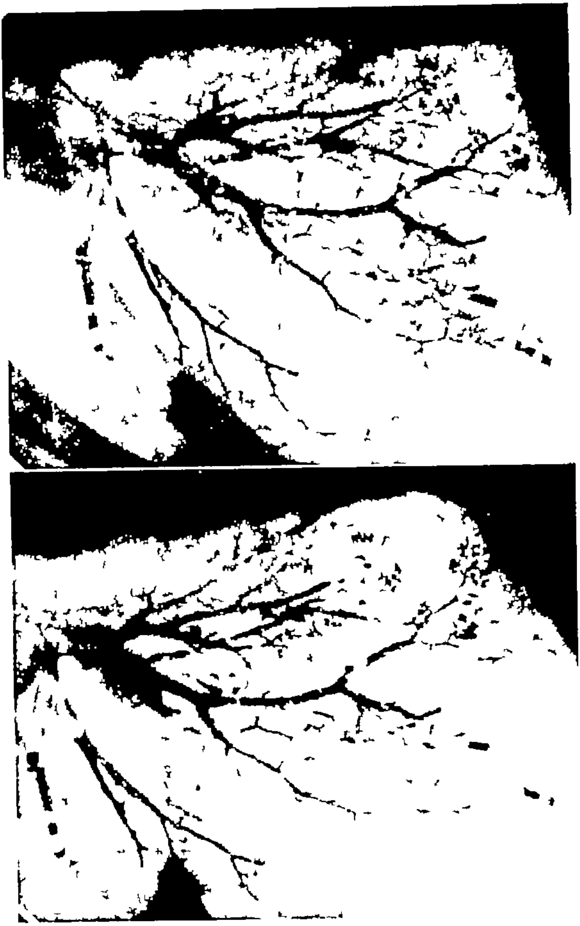
No 1 No 2

Fig 1 Radiograph No 1 Taken at the End of Inspiration, Radiograph No 2 Taken at the End of Expiration

All the bronchi and bronchioles are decidedly larger in No 1

FIG 2 RADIOGRAPHS TAKEN DURING THE COURSE OF NORMAL RESPIRATION, NO 1 NEAR THE END OF INSPIRATION, NO 2 NEAR THE END OF EXPIRATION

The bronchi in No 1 show little or no change in calibre compared with No 2



No 1 No 2

Fig 3 Radiographs Taken during the Course of a Normal Respiration No 1 during Inspiration, No 2 during Expiration

Some of the long bronchi in the right lower lobe are narrower than the corresponding bronchi during expiration

greatest at the beginning of inspiration, at the time of the descent of the diaphragm, especially with respect to the lower lobes Radial traction would be greatest at the end of inspiration upon elevation of the ribs, when the antero-posterior and lateral diameters of the lungs are at a maximum During quiet respiratory movements the tendency to widen during inspiration due to radial traction is prac-

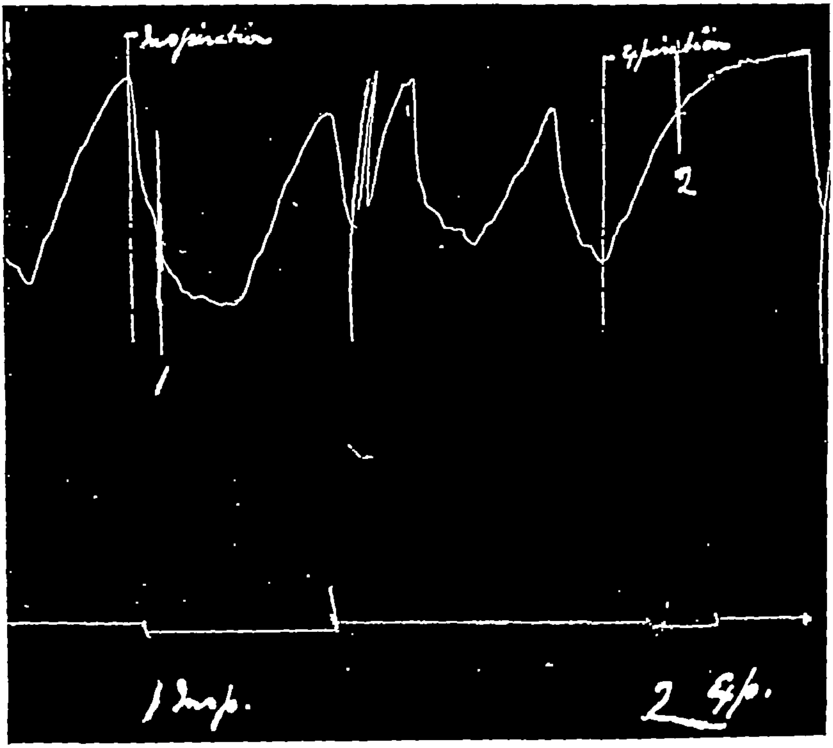


Fig 4 Upper Tracing Indicates Respiratory Movements, Down Stroke Inspiration Upstroke Expiration

The lower line indicates the time of exposure of the x-ray films

tically equalled throughout the greater portion of the lungs by the tendency to narrow due to linear traction

To study the passive changes which might occur in the bronchi during inflation and deflation of the lungs, experiments were performed on two cats after death The recently killed animal was placed in a large rigid cardboard paper cylinder so fitted that exhaustion of


No 1

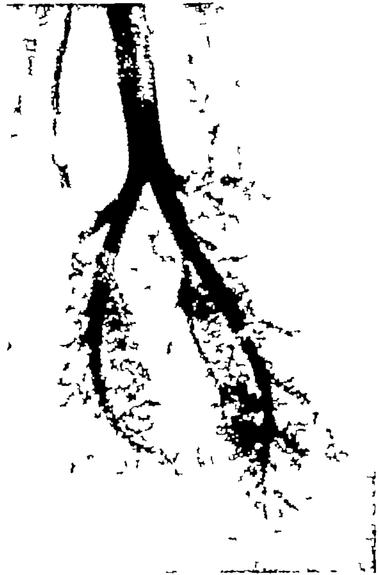

No 2

Fig 5 Radiographs of Dead Cat, No 1 Taken with Lungs Fully Deflated, No 2 during Partial Inflation
Note the lengthening and narrowing of the main bronchus to the lower lobe

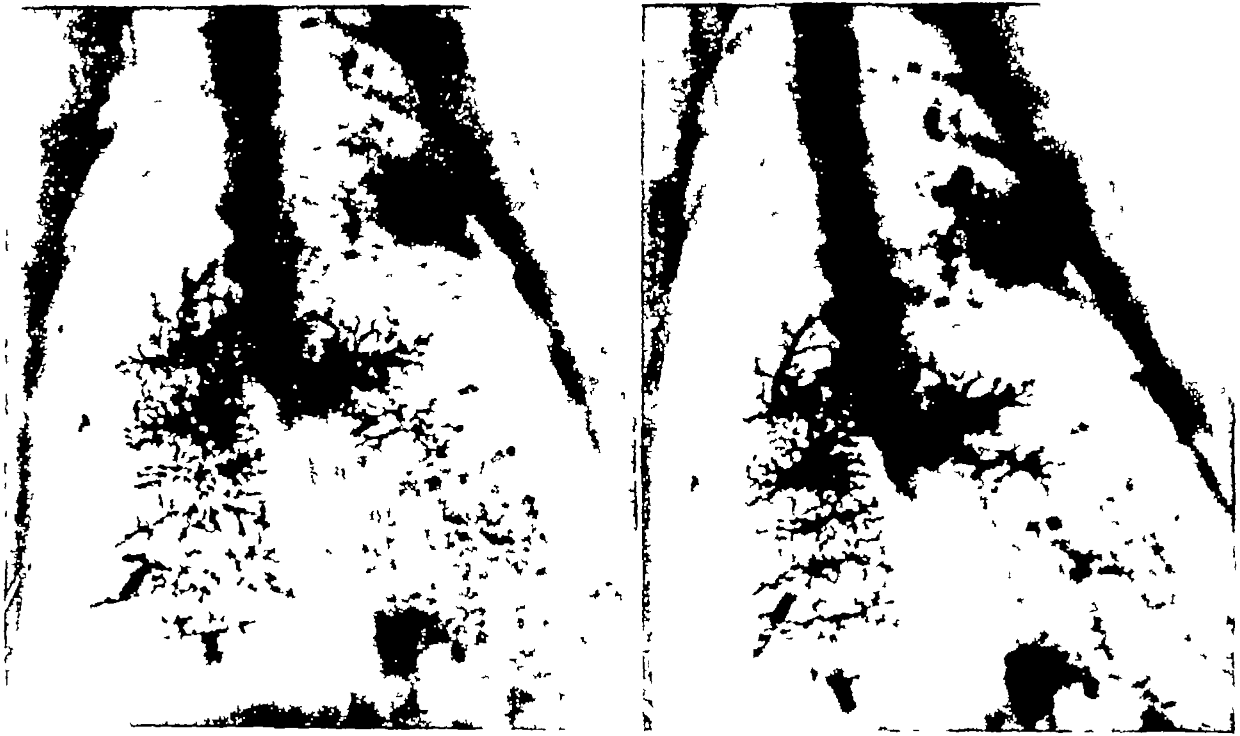


Fig 6 Radiographs of Dead Cat, No 1 Lungs Inflated to a Greater Degree than for Either of the Films of Figure 5 and also to a Greater Degree than for No 2

Note that the bronchi and bronchioles in No 1 are of larger diameter than in No 2 Many of the very small bronchioles are clear enough for comparison

the air within the cylinder by a water suction pump was possible A tracheal cannula, firmly tied in, opened to the atmosphere through a rubber stopper in the lid of the cylinder Through the cannula the lipiodol was administered Radiographs were taken with the cat's lungs inflated and deflated by negative pressure to varying degrees A paper cylinder was used because it interfered with the passage of the x-rays less than glass

Figure 5 shows two films obtained in this manner They show definitely that the elongated bronchus to the lower lobe is somewhat narrower in the inflated lung (film no 2) than the same bronchus in the collapsed lung (film no 1) With a greater, but not excessive degree of inflation, the bronchi are larger in the more inflated lung (film no 1, fig 6) The small bronchioles are well shown in these last two films and are definitely larger in the more inflated lung One sees therefore that the longitudinal and radial changes demonstrated in the radiographs of the living lung can be paralleled in the dead lung where they are entirely passive

The sequence of passive changes then seems to be as follows, with deflation, bronchioles shortened and narrowed (fig 5, no 1), with partial inflation, elongated and possibly further narrowed (fig 5, no 2 compared to no 1), and with more extensive inflation, widened (fig 6, no 1 compared with no 2) In the living lung any active influences would be superimposed on the changes induced by passive forces The presence or absence of active influences in ordinary respiration can not be determined from the evidence at hand

These changes of caliber and length are quite in keeping with anatomical considerations Miller (1924–5) has described the course of the muscular fibers of the bronchi and shown them to circle the opening somewhat obliquely The elastic fibers run lengthwise The latter would then be the chief factor controlling lengthening and shortening of the bronchi, but, in addition, change of tone of the circular musculature, if it occurs, may either add to, of compensate for the passive effects due to radial traction, and may thus alter the diameters of the bronchi If there is no active participation on the part of the bronchial musculature in ordinary respiration it would still exert its influence as an elastic structure the degree of stretching of which would vary with the degree of vagus and sympathetic tone

Numerous researches have shown that the calibre of the bronchi is under nervous control Vagus stimulation causes constriction, sympathetic stimulation dilatation (Weber, 1910) L A Muller (1910) has demonstrated the presence of ganglion cells in the bronchial walls With the lipiodol method we hope to investigate the question of active changes in the tone of the bronchial muscles during normal respiration and if changes occur to determine the nervous mechanism involved There does not seem to be any reason why the method described should not also be applicable to studying changes occurring in asthma

SUMMARY

A method is described for demonstrating changes occurring in the calibre of the bronchi during normal respiration

The bronchi and bronchioles are widest at the end of full inspiration, narrowest at the end of full expiration The changes are apparent chiefly at the end of the full inspiration and the beginning of the full expiration Within the limits of quiet respiratory excursions there is practically no change in the calibre of the bronchi except during the early part of inspiration when some of the longer bronchi, particularly those to the lower lobes, are actually narrowed Both narrowing and widening can be explained on a passive basis, as resultants of linear and radial tractions, the character and relative degree of which are determined by the manner of enlargement of the thoracic cavity during respiration No evidence is available at present to determine the presence or absence of any active influences involving bronchial muscle tone

The writer wishes to express to Dr Joseph Erlanger and to Dr George H Bishop his appreciation for their supervision of this work

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GENERALIZED MYCOSIS DUE TO A HITHERTO UNDESCRIBED FUNGUS (GLENOSPORA GAMMELI)

By M A BLANKENHORN AND JOHN A GAMMEL

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(Received for publication May 4, 1927)

Case reports of generalized mycosis are infrequent, first, because the condition is probably not very common, secondly, because few clinicians are interested in this type of disease and do not possess the training necessary to study the fungi, and thirdly, since Koch's postulates cannot be fulfilled in dealing with diseases due to fungi, pathologists and bacteriologists hesitate to make clinical reports on incomplete studies

We report this case because we believe it to be an instance in which an apparently harmless, though hitherto unrecognized mould has invaded the tissues of man and produced a serious disease, which once recognized, could be treated satisfactorily Furthermore, we think that the detailed description of the method of identifying the strain of this fungus may serve as a guide to others in similar investigations

CASE HISTORY

The patient, aged forty five years, walked into the dispensary of Lakeside Hospital in March 1925, complaining of pain in the chest, cough with bloody expectoration and loss of weight This he had endured for about four months thinking that it had started from a cold, and although unable to work he had not come for medical aid until very recently he had been alarmed by seeing blood in his stools He had had the malaise and weakness common to destructive lung disorders but no night sweats He looked quite ill and could scarcely speak on account of persistent cough He could give no definite account of the appearance of certain skin lesions other than that they had been present for not more than four weeks

He had had no previous illnesses and had worked steadily as a coal miner, but immediately before becoming sick had worked at heavy outside construction pouring concrete Examination showed that he had a partial consolidation of

his right upper lung with coarse and fine moist râles suggestive of pulmonary tuberculosis

At various places within the skin or under the skin there were lesions not compelling interest, until more carefully investigated They occurred in three forms (figs 1 and 2) On his back, face and neck they were like furuncles but with much necrosis and little inflammation, they were not tender nor had they been painful Other lesions of the face back, neck scalp, soft palate and tongue

FIG 1 ULCERATING GRANULOMATOUS LESION OVER RIGHT SCAPULA Below and to left two small papules

were more tumorous in nature, with no necrosis or inflammation They seemed to be within the skin or just beneath the mucous membranes, where they could be seen as yellowish-gray, soft bodies, from 3 to 10 mm in diameter They were not tender The third type of lesion was larger and lay deeper These were soft, movable and semifluctuant, being more like lipomata than any other common condition One such 5 or 6 cm long, was attached to the sheath of the right triceps another in the right biceps one over the right deltoid near its lower inser-

tion and another on the anterior aspect of the right thigh The axillary and supraclavicular lymph nodes of the right side were definitely enlarged and quite hard All these lesions increased in size so that a few of the cutaneous nodules softened and ulcerated within a few days and some of those already ulcerated about the face crusted over in a manner to resemble blastomycosis This diag

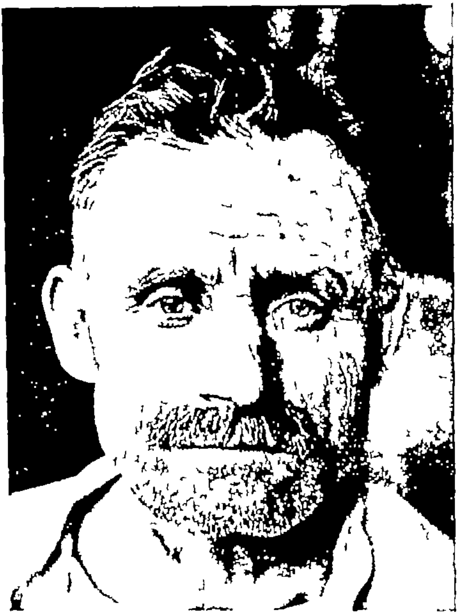


FIG 2 LESIONS ON FACE TWO SMALL PAPULES ON FOREHEAD, LARGER CRUSTED LESION ON LEFT EYEBROW, ONE DEEP SEATED NODULE ON LEFT SIDE OF CHIN

nosis was made by the dermatologist consulted Careful examination of his heart and central nervous system showed no signs of syphilis

His temperature averaged 38°C , going as high as 38.5°C practically every day The blood, except for a leukocytosis of 10,000, showed nothing abnormal and the Wassermann reaction was negative Urine was likewise negative The sputum was very purulent and bloody and contained a few undetermined organisms, but

no acid fast bacilli or fungi Material from several lesions showed no forms whatever suggestive of fungi The stools throughout his stay in the hospital were entirely normal

Roentgen-ray of the chest was reported as follows (fig 3) "Stereoscopic films of the chest show a roughly triangularly-shaped shadow of increased density, extending outward from the right hilum There seems to be some exaggeration of the bronchial markings and some haziness of the right apex The right dia-

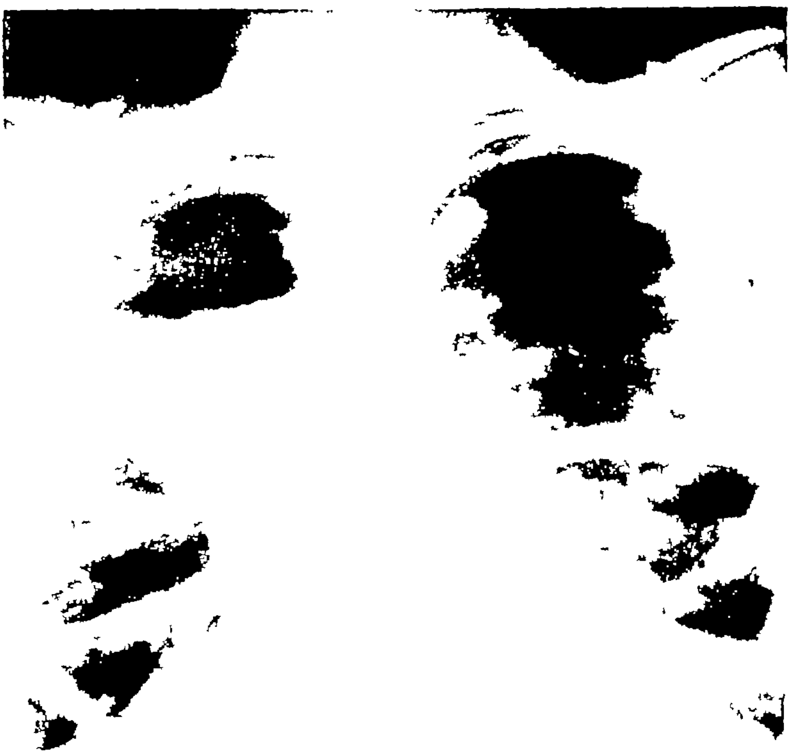


FIG 3 X-RAY SHOWING TRIANGULAR SHADOW EXTENDING OUTWARD FROM RIGHT HILUS

phragm seems somewhat deformed, probably in part by adhesions The appearance on the right looks distinctly more like a neoplasm than an infectious process such as tuberculosis The trachea is seemingly pulled well to the right There is apparently an anomaly in the form of the first left rib, the entirety of which is not shown on these films —C M"

Cultures made from under a large crust on the face showed a white fungus in all media Cultures taken by aspiration from several deep tumors and cultures

made from tumors removed surgically yielded the same fungus. Blood cultures were negative

Lesions removed for biopsy were reported once as granuloma and again as chronic inflammatory tissue. The larger lesions removed from the muscles proved to be abscesses, filled with thick, greenish pus in which no organism could be identified

The patient was given as medication iodide of potash in 5 grain doses three times each day, and neoarsphenamin to a total of 4 65 grams Protein shock with vaccines of *Bacillus typhosus* caused no reaction either locally or systemically

Under treatment the skin lesions healed promptly, the fever subsided, as did the cough and expectoration Physical signs and x ray showed the condition of the lungs to be much improved

He was discharged from the hospital after sixty-one days as entirely well, and has been working in the mines ever since.

ESTABLISHMENT OF THE STRAIN

On April 7, 1925, we attempted for the first time to isolate the organism which we believed to be a blastomyces or sporotrichum As media for all primary cultures we used ordinary glucose agar and Sabouraud's milieu d'épreuve Pus from the small follicular abscesses in the periphery of the lesion on the left eyebrow was used for inoculation Other culture tubes were inoculated with the material from a nodule on the right shoulder This lesion resembled more an unopened furuncle Pus was aspirated with a sterile syringe after careful preparation of the skin, and cultured Six tubes were incubated at 37°C, the other 6 were kept at room temperature

After four to five days some of the tubes at room temperature showed colonies of a fine white mycelial growth spreading slowly toward the periphery During the next few days the same growth was noticed in 10 tubes One tube was contaminated with *Staphylococcus albus*, 1 remained sterile The tubes in the incubator showed a much slower growth

On April 12, a second series of cultures was made in the same way using this time only the aspirated material from two superficial, fluctuating, closed abscesses A pure culture of a white mold grew in all tubes

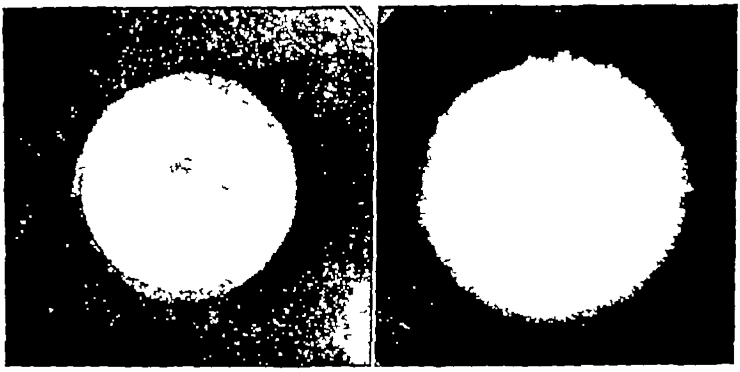
On April 21, a third series of cultures was taken The material was obtained under most rigid precautions by puncturing an abscess of about a walnut size about 2 cm below the skin in the biceps of the

right arm The same growth as in the first and second culture series resulted

When the first biopsy was performed, cultures were also made by the surgeons on the routine media The pathological laboratory reported "no growth after forty-eight hours" but when the cultures were reexamined about ten days later and compared with our first cultures, a white mold was noted

Smears from the pus showed only polymorphonuclear leukocytes, but no organisms of any kind

During the following weeks cultures of these four series were studied and compared They were found identical on macroscopic



FIGS 4 AND 5 CULTURES ON SABOURAUD'S GLUCOSE PEPTON AGAR THREE WEEKS OLD

and microscopic examination, therefore, only the strain obtained on April 21, was used for the further mycological study

Macroscopic examination The fungus was successfully cultured on almost all available culture media as plain agar, glucose agar, Sabouraud's milieu d'épreuve and de conservation, Grütz Nervina Malz Pepton Knoll agar, Löffler's serum agar, endoagar, potato, human serum, gelatine, whole milk, litmus milk, plain broth, Sabouraud's glucose pepton broth, pepton water, potato water, and several litmus sugar media The only medium where no growth could be obtained was Raulin s fluid for molds

The mycelium on Sabouraud's glucose pepton agar consists of a dense, thick, rather undifferentiated feltwork of delicate hyphae with an occasional tendency to concentric arrangement In Erlenmyer flasks the central portion may become elevated, knoblike, and often fissured The colony forms usually an almost per-

fect circle although at times the periphery may assume a rather irregular wavy appearance The color varies from white to light brown and yellowish brown. Cultures on Sabouraud's glucose agar three weeks old have a diameter of 26 to 32 mm. (fig 4)

On Sabouraud's maltose agar the mycelium remains almost white and shows less tendency to spread The growth is much slower

On top of old cultures on Sabouraud s proof media, sometimes a white duvet is noted Pure white duveteuse growth as in the polymorphic form of trichophy tons etc is frequently observed (fig 5) but experiments have shown that in sub cultures the brown growth and the forms observed in our first cultures can be obtained again Therefore, we believe that we are here dealing only with simple individual variations, id est pleomorphism of this organism A true poly-morphic form as established so well by Sabouraud for most ringworms was not observed

The most luxuriant and brilliant growth occurs on Grütz Malz agar where the color may become brown

On ordinary glucose agar a heavy, uniform white growth is obtained with a marked tendency to radiate from the center and spread peripherally far beyond the margins of the nutrient substratum. The hyphae frequently cover the walls of the culture tube with a hazy network

On Löffler's serum agar, endoagar, egg agar Sabouraud s milieu de conserva tion, the mycelium is white and of varying density The concentric and radial arrangement is less pronounced or absent The hyphae as a rule do not project beyond the medium On Sabouraud s pepton agar the color is grayish white

The growth on agar is limited the colonies remain white, small and button like

The upper portions of carbohydrate media darken slightly The fine rhizoidal hyphae invade the medium only superficially

In liquid media our fungus forms a powder puff like growth on the bottom of the culture tubes or flasks and ascends later to the surface There it finally forms a thick white membrane that seals the culture fluid. Sometimes, on milk for instance a growth appears only on the surface The location of the growth seems to depend chiefly on the specific gravity of the medium.

The aspect of the cultures on Sabouraud s as well as on other solid media, is subject to variations within certain limits even if all cultures are made and kept under exactly the same conditions No conclusions as to identity can be drawn from the macroscopic findings

Microscopic examination Material of cultures on solid media was soaked in 40 per cent KOH, teased and examined Cultures on glucose agar and Sabour-aud s milieu d'épreuve were embedded in paraffin and serial sections stained with hematoxylin eosin. Hanging-drop cultures with Sabouraud s glucose pepton broth or a medium where the French glucose masseé de Chanut was replaced by the American glucose Pfanstiel showed the process of reproduction in the most satisfactory way The mycelium climbing up the walls of the culture tubes was also examined

The hyphae are cylindric tubes with apical growth, transversely septate, rather straight, hyaline or subhyaline, filled sometimes with a few fine granules or also occasionally with droplets The young mycelial filaments are undivided by partition walls Old filaments are hyaline and also in these the septa are frequently invisible The diameter of the hyphae varies from 2 to 5 3 micra, the interseptal segments have a length from less than 15 to 103 micra The branching occurs laterally and sometimes by dichotomy Some thick hyphae form a mycelium "en raquette" as known in *Microsporon Audouini* and other fungi There is a

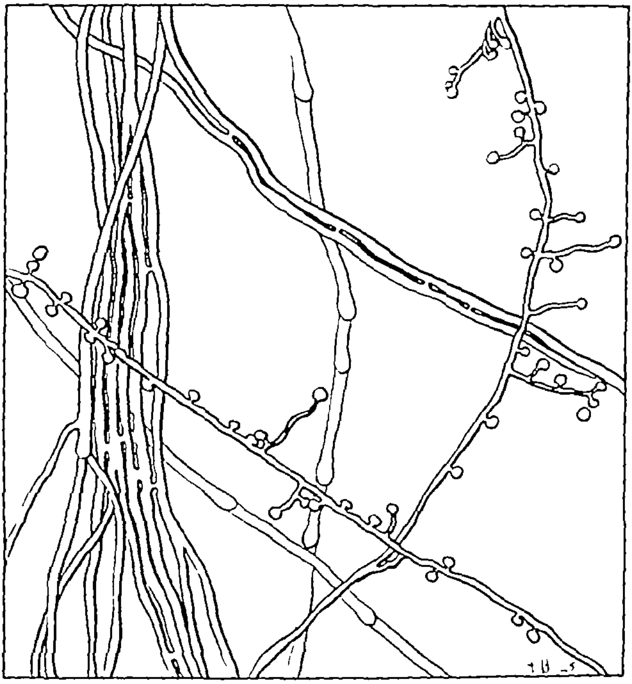


FIG 6 DRAWING OF HANGING DROP CULTURE HYPHAE OCCASIONALLY IN COREMIA-LIKE BUNDLES WITH INTERLACING BRIDGES ALEURIOSPORES EITHER SESSILE OR BORNE ON SPOROPHORES "MYCELIUM EN RAQUETTE"

marked tendency to form coremia and these hyphae are frequently connected by short bridges (fig 6) Floating of the protoplasma and Brownian movement of the fine granules in the interior of the fungus could be noted

The spores are conidia They are sessile and usually attached directly to the sporiferous hyphae (pleurogenous) or are sometimes borne on simple erect sporophores of 1 6 micron diameter and varying length These sporophores are unseptate and barely *differentiated from the hyphae* They as a rule bear a single terminal spore, but exceptionally one sporophore may support two or three spores,

the second and third one then being lateral to the axis Short sporophores may suggest phialides

The size of the conidia varies from 3.3 to 6 6 micra with an average diameter of 4 2 micra (fig 7) They are in young cultures, pale green, usually one-celled, homogeneous or filled with small granules, spheric or slightly ellipsoidal with smooth walls In older cultures the shape of the spores becomes more irregular, they may be filled with globules, and two-celled spores are occasionally observed

One mycelial segment may give rise to several of these spores Where the walls

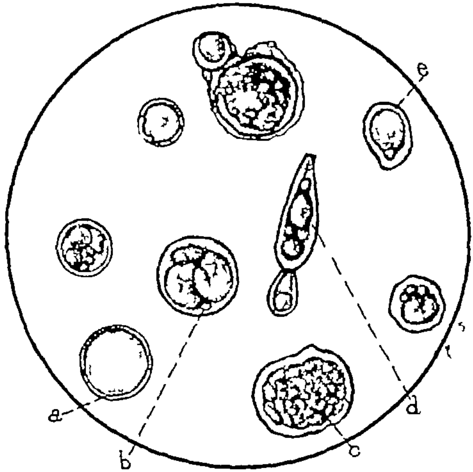


FIG 7 VARIOUS FORMS OF CHLAMYDOSPORES

of the hyphae bud spores short chains are sometimes noted The spores are cut off very late and always remain close to the hyphae from which they originated

Hyphae and spores may be concolorous, but usually the spores are darker than the mycelium, especially in the old cultures

Large globose spores of 10 to 12 micra diameter, and darker than the ordinary spores, are found in some old hanging-drop cultures and in teased preparations from old cultures on solid media They are usually terminal but show occasionally also an intercalary position The wall may become thickened, double-contoured (fig 7 a) and a round or oval body may be formed (fig 7, c) Sometimes

coarse, rather regular granules of 1 6 to 2 micra diameter fill these cells and the color changes gradually to brown In some of these cells the granules may disappear again while a two or three-celled spore remains (fig 7, b) Some of these spores resemble somewhat the oospores of *Peronospora viticola* At no time, however, were organs suggesting sexual reproduction seen No opening in the wall or its rupture was noted, therefore, we interpret them as chlamydospores

In parts of cultures where the formation of conidia is sparse or absent, the ends of a few mycelial filaments may form a loop (fig 8) or become spirally twisted Neighboring hyphae, single or in bundles, interlace with them and form finally an irregular, round or egg-shaped body of 43 to 85 micra diameter In cultures on glucose agar they may be stalked These bodies are very rare, but were found in old hanging-drop cultures as well as on the walls of tubes containing cultures

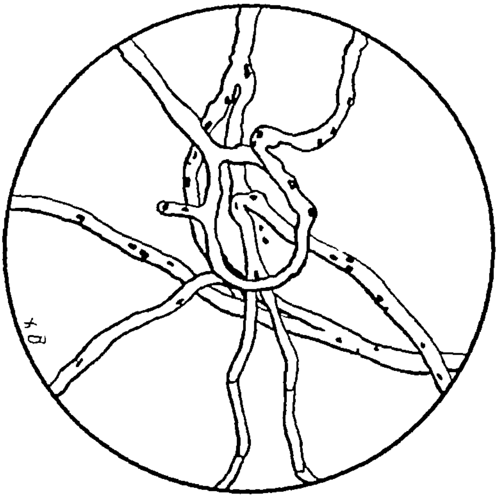


FIG 8 MYCELIUM WITH BEGINNING LOOP FORMATION

on solid media They suggest somewhat loose rudimentary perithecia analogue the "organes nodulaires" or minute sclerotes In this connection, of course, we do not think of sclerotes as of the highly organized resting bodies of hyphae in the strict definition of Anton de Bary, but we employ the term here in the wider sense as it is used in the French and American medical mycological literature When studied under high power (fig 9) they appear as gray or light brown bodies consisting of closely packed mycelium An opening could not be observed, their significance could not be made out

All attempts to study perithecia in sections failed Sections of cultures on solid media fixed in formalin and embedded in paraffin give a rather uniform appearance, small threads (caliber 1 3 to 1 6 micron) and abundant globose bodies

of a diameter of 11 to 12 5 micra with a thick wall Some have a slightly granular appearance (chlamydospores)

Since Nannizzi (1) in Pollacci's (2) Institute succeeded in recent years in revealing the ascospore stage of certain hyphomycetes as *Trichophyton*, *Microsporon*, *Achorion*, etc., by culturing these organisms on bird feathers, skin, hair and bones, we attempted to grow the fungus isolated by us on chicken feathers and human hair, however, without result

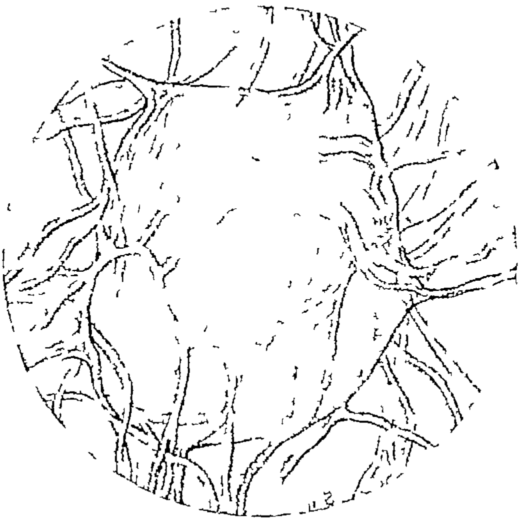


FIG 9 SCLEROTIA LIKE STRUCTURE FORMED BY DENSELY INTERLACED MYCELIUM

Chemical action The fungus produces in the media a marked alkaline reaction The blue color in litmus milk and litmus broth is deepened considerably Litmus milk is cleared and assumes a port wine tint In old liquid cultures the envelope crystals of calcium oxalate and other crystals suggesting monocalcium phosphate may be found

Ferment production Litmus broth with dextrin, maltose, mannite and saccharose, does not change its color Lactose litmus broth assumes a slight port wine tint. Litmus broth with galactose, glucose and levulose, is very slowly decolorized

after the fourth week No gas formation in any of the litmus sugar media was noted The fringe of the otherwise white mycelium that is in contact with the wall of the culture tube assumes a deep blue color

Gelatin is liquefied after three to four weeks, a dense yellow mycelial growth covers the surface Brown pigment diffuses from it down into the translucent medium and darkens it slowly The bottom of the culture tube is covered with a fine sediment

Coagulated human serum exhibits surface growth

Whole milk does not show any change during the first two weeks except for a heavy growth on the surface, no coagulation takes place After four weeks the milk has a light yellow color and is turbid After eight weeks the fermentation is completed The fluid is clear and dark yellow with a brown tinge A light brown growth fills the upper third of the medium, while a coarse, heavy flocculent precipitate covers the bottom of the tube

The optimal temperature is between 18° and 22°C Development in the incubator at 37°C is slow and very poor, this did not change the subcultures

The fungus is strictly aerobic The development of young cultures in broth was immediately inhibited when the fluid was sealed with a thick layer of vaseline

Growth in bouillon over chloroform was slightly restrained Old cultures have a slight fecal odor

The organism is Gram-negative Some parts, however, may take the stain occasionally It tinges readily with the usual laboratory dyes, Sahli blue, eosin, etc The most satisfactory preparations probably were obtained with highly diluted fuchsin

Agglutination and similar tests were not carried out

Animal experiments in a monkey, 2 guinea pigs and 7 rabbits, with pus from the lesions and suspensions from cultures, failed to reproduce the disease

CONCLUSIONS

It is obvious that as the fungus in question is a parasite with septate filaments, and reproducing by spores it belongs to the *Eumycetes* of Schroeter 1892 Until the formation of asci and perithecia is proved, it is equally manifest that it must be placed in Fuckel's class (1869), *Fungi imperfecti*, and in Vuillemin's subclass *Hyphales* According to the modus of spore formation it belongs to order *IV Conidiosporales* Vuillemin 1910

When we reported our clinical and mycologic observations before the Association of American Physicians in May, 1926, we suggested that the fungus should be placed in the suborder *Aleuriosporineae* Since the necessary mycologic literature for further classification was not at our disposal, we sent the organism together with our report

to the director of the Institut of Botany of the Royal University of Siena (Italy) for identification which Professor Gino Pollacci and Professor Arturo Nannizzi very kindly performed These mycologists verified our findings and agreed with our tentative classification Since they considered it as a hitherto undescribed species they proposed for it the name of *Glenospora Gammeli*, which they define as follows

"*Glenospora Gammeli* sp n Pollacci et Nannizzi —Hyphis sterilibus hyalinis vel subhyalinis, rectis, cylindricis, saepe guttulatis, junioribus continuis, adultis plus minusve distincte transverse septatis, 2 to 5.3μ diam segmentibus 15 to 100μ long, monopodice ramosis, nonnumquam dichotomis, majoribus crebre septatis, articulis clavatis ut in *Microsporo Audouinio* et aliis micetis specierum, haud raro fasciculatis, hinc inde anastomo ibus brevibus inter se connexis, hyphis fertilibus concoloribus decumbentibus, paullo tenuioribus, varie breve ramulosis, superne aleuriis acro-pleurogenis gerentibus Aleuriis sessilibus vel aleuriophoris longitudine varia suffultis, sphaericis, levibus, initio 3.3 to 6μ diam hyalino-chlorinis, postremo majoribus, 10 to 12μ diam., crassiuscule tunicatis, granuloso farctis, ramulis diu haerentibus, dilute luteo-fuscis

Hab in cute hominis, Cleveland, Ohio, America borealis (Gammel) Coloniis (in agaro glucosato Pollacci) initio rotundis, applanatis, candidis, byssineis, concentrice zonulatis dein confluentib s, interdum luteolis vel brunneolis, in senectute crustam applanatam matrice arctiuscule adnatam efformantibus"

In an additional note Professor Pollacci and Professor Nannizzi state that according to their investigations *Glenospora Gammeli* produces one single kind of reproductive elements, i e, aleuria These become separated from the mycelium very late, and at maturation they become enveloped by a membrane of their own The membrane belonging to the portion of hypha in which each of them was formed becomes lacerated and drops off Outlines of perithecia or sclerotia such as we described were not observed by the Italian mycologists

The genus *Glenospora* belongs to the suborder *Aleuriosporineae* of the order *Conidiosporales* It was originally published by Berkeley and Curtis (3) with a very few words "Flocci fastigiati fasciculati parce articulati, hic illic sporangia globosa sessilia vel pedicellata ferentibus" Saccardo's (4) description is also brief "Hyphae biogenae, in crustam atram intextae, varie ramosae, septatae Conidia ramulis diu haerentia, globosa, majuscula, levia"

Several species of this genus have been found already as pathogenic for man (5) *Glenospora graphii* was observed in otomycosis by Hassenstein, Bezold, Hallier, Stendener and Siebenmann Morax and Pinoy isolated it in 1910 from a case of keratomycosis *Glenospora Semoni* and *Glenospora khartoumensis* were found producing maduromycosis of the black grain type Henseval in Ghent isolated an organism from the sputum of a fetid bronchitis, which was studied by Vuillemin and termed *Glenospora gandavensis*

Other species of the genus *Glenospora* as *G Curtisii*, *G ramorum*, *G sacchari*, *G microspora* are known as plant parasites (6) During the last year we attempted to culture our fungus on small pieces of bark and wood of certain trees (beech, cherry, ash, hickory, soft maple), however, without result

The way the culture material was obtained and the course of the disease entitle us to pronounce *Glenospora Gammeli* in the case described as pathogenic We do not think that all requirements of Koch's law can be fulfilled in diseases caused by fungi

We desire to express our gratitude to Professor Gino Pollacci and Professor Arturo Nannizzi of the Institute of Botany of the Royal University of Siena (Italy) for the classification of this organism

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THE RATE OF GASTRIC SECRETION IN MAN

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The lack of methods for estimating accurately the volume of gastric secretion in man has made it difficult to determine just how much gastric juice is produced by the stomach in response to various stimuli Clinicians have generally assumed, however, that after the introduction of food or other stimuli secretion gradually increases, and reaches a maximum only after an interval which may be as long as an hour or more. This view is evidently based on the titration of acid values of specimens removed from the stomach during the course of a "fractional analysis "

The literature on the types of "acid curve" obtained by the fractional Rehfuss meal is reviewed by Crohn and Reiss (1) It may be recalled that isosecretory, hypersecretory and hyposecretory types are distinguished on the basis of the degree of acidity and the time after the introduction of the test meal when the high point is reached. Still other types of curve have been related to various gastric disorders

The ordinary fractional method of gastric analysis yields, however, only the vaguest information about the volume of gastric juice, nor do the usual rising curves of acidity have any constant relation to the acidity of the actual gastric juice inasmuch as the titration values are modified by two unknown factors, namely, the rate at which the test meal is diluted by gastric secretion and the rate at which the stomach empties In brief, the conventional methods of gastric analysis do not tell whether gastric secretion gradually increases after stimulation, or whether stimulation is promptly followed by a maximum response both as regards volume of secretion and degree of acidity

By means of a method which we recently described (2), it is possible to estimate the acidity of the pure gastric juice as well as the volume of gastric juice secreted in successive ten minute periods after stimu-

lation by 50 cc of 7 per cent alcohol The results indicate that under the conditions of these observations gastric secretion usually begins promptly after stimulation and is almost immediately at a maximum, both as regards amount and acidity, and that the slow evolution of gastric secretion, which is generally believed to be the rule, rarely takes place

MATERIAL AND METHODS

Observations were made in a consecutive series of people Some were "normal," some were ill with digestive or other disorders

The method for testing gastric activity after introduction of 50 cc of 7 per cent alcohol into the stomach was used exactly as previously described (2) The amounts of gastric secretion produced during successive ten-minute periods after stimulation were determined, as well as the titratable acidity (in terms of cubic centimeters of N/10 NaOH, with phenolphthalein as indicator) of the pure juice

The method is, briefly, as follows

The subject should take no food during the twelve hours preceding the test If possible, he should be under "basal" conditions, i e, resting quietly in bed

A duodenal tube is passed to a distance which will allow the tip to reach the most dependent part of the stomach The fasting juice is withdrawn at five-minute intervals for fifteen or twenty minutes Then, without attracting the patient's attention, 50 cc of 7 per cent alcohol to which 0 5 cc of 1 per cent alcoholic phenolphthalein has been added is injected by means of a large glass (100 cc) syringe through the tube into the stomach The entire gastric contents are then immediately withdrawn, measured in the syringe and reinjected, save for 10 cc which are kept for analysis The patient is kept in a semirecumbent position, but during the aspiration is turned on both sides in order to make complete emptying of the stomach more certain Ten minutes after the first aspiration, the stomach is again completely emptied, the contents are measured and returned except for the 10 cc sample for analysis This procedure is repeated at ten-minute intervals for one hour or until the stomach is empty (contents less than 10 cc) It is very important that saliva is not swallowed during the test

The samples are usually clear and limpid and are highly satisfactory for study

The volume of gastric juice secreted in any ten-minute period may be calculated as follows

As pointed out above, phenolphthalein has been added to the alcohol test meal The various specimens aspirated at ten-minute intervals may be made alkaline, thus bringing out the red color of the dye, the concentration of which can then be readily determined by reading against a standard in a colorimeter In this way

the percentage dilution of the gastric contents at various intervals is calculated Knowing this, and knowing the total volume of stomach contents at the beginning and at the end of each ten minute period, the maximum and minimum possible volumes of secretion which would satisfy these figures can be calculated by the following formula $[(\frac{x}{y} \times A)] - A$ = maximum possible amount of juice secreted in ten minute period, and $B - [(\frac{y}{x} \times B)]$ = minimum possible amount in which A equals the number of cubic centimeters of fluid in the stomach at the beginning of the period, B, the number of cubic centimeters at the end of the period, x the concentration (percentage reading) of phenolphthalein at the beginning of the period, and y, the concentration at the end

The actual amount of secretion evidently lies between the calculated maximum and minimum possibilities These usually agree quite closely, so that an average can be taken which must be very near the true figure In certain cases, however, especially when the stomach empties very quickly, the maximum and minimum values are so far apart that conclusions cannot be drawn as to actual volume of secretion If the test is repeated on another occasion, satisfactory figures may be obtained

The acidity of the pure juice present in the stomach at the time of each aspiration can be determined by the usual method of titration with a correction for dilution by the test meal on the basis of the percentage of dye present at the time A more detailed statement of the technique may be found in the previous paper

RESULTS

The rate of gastric secretion after stimulation

In table 1 and chart 1 are shown the volumes of gastric secretion during successive ten-minute periods after introduction of the alcohol meal One sees that on the whole the volumes tend to decrease rather than to increase as time elapses after stimulation Case 76 was an exception in so far as after forty minutes there was a marked increase in secretion This patient had a duodenal ulcer In a composite chart (no 2) are shown the sums of the volumes of secretion for four ten minute periods in all the cases in which complete observations over this length of time were available This shows even more clearly the initial high value which tends to fall and not to rise

The curve of acidity after stimulation

Table 2 and chart 3 show the corrected titratable acidity of the pure gastric juice before stimulation and at ten minute intervals after

introduction of the alcohol meal In nearly every instance the juice attains its maximum or nearly its maximum acidity within ten minutes after stimulation regardless of the fasting value If allowance is made for the error inherent in the methods one may conclude that stimulation is followed almost immediately by a secretion of maximum acidity, the actual level attained may be high or low In occasional cases (nos 92, 198) there was a continued steadv rise, but this was never

TABLE 1

Volumes of gastric secretion for ten-minute periods after alcohol meal

Case number	Diagnosis	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
		cc	cc	cc	cc	cc	cc
156	Gastric ulcer	59	52	57			
92	Normal	47	52	49	33	22	
76	Duodenal ulcer	43	36	40	31	67	71
198	Normal	27	40	15	29	17	
178	Chronic myocarditis	27 5	24	18	12	11 5	8
180	Congenital syphilis	27	17 5	12	6 5	3	
146	Psychoneurosis	25 5	30 5	31	26	38	
236	Normal	25	21	16			
80	Normal	24	15	13	13	12	11
54	Bradycardia	24 5	20	11	9 5	7	
84	Normal	22	10	10	18 5	16 5	6 5
196	Normal	21	16	20	15	7	
122	Normal	20	17 5	14 5	7 5		
86	Normal	19	14 5	19 5	15	8 5	
106	Arteriosclerosis	14	11 5	15 5	8	5	5
94	Arteriosclerosis	10	12	13	6	5 5	
214	Normal	14 5	24 5	11 5	18 5	8 5	
174	Chronic peritonitis	12 5	10	10 4	7 8		
304	Gastric ulcer	23	53	30	18		
222	Psychoneurosis	23	25				

extreme in proportion to the initial rise immediately after stimulation In a few other cases, on the contrary, the acidity seemed to fall from the start (nos 106, 146) A composite chart (no 4) confirms the essential features of the individual curves

It appears, therefore, that the "alcohol meal" is followed not by a gradual evolution of gastric secretion but by a prompt and often maximal response, and it is important to reconcile these findings with

those of the ordinary fractional meal, which usually shows a progressive rise in acidity Several sources of error in interpretation are to

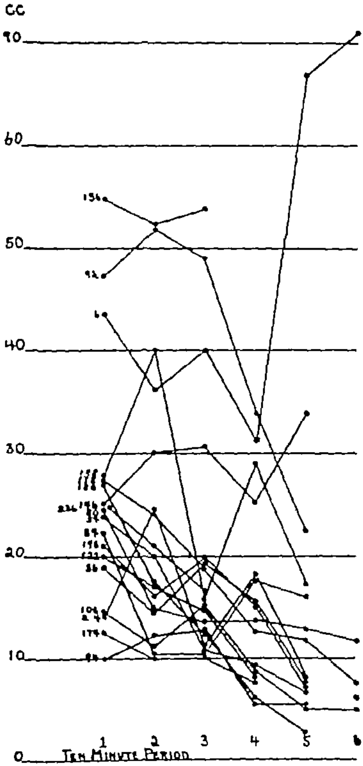

CHART 1 VOLUME OF SECRETION FOR TEN MINUTE PERIODS AFTER ALCOHOLIC MEAL

be considered In the first place, as emphasized by Gorham (3), the acid actually secreted by the stomach is diluted by the fluid of the test meal Clearly the acid values of specimens withdrawn at various

intervals will depend not only on the amount of secretion but on the speed with which the test meal leaves the stomach If the emptying is rapid a high acid value will be reached more quickly than if the diluent is retained in the stomach in large quantity Furthermore the buffer action of saliva and of the test meal mask the presence of acid until an excess has been secreted In order to bring out the point more concretely the following experiments were done

Experiment 1 The usual (Ewald) test meal of two slices of bread and 500 cc of water was prepared, but instead of swallowing the meal, the patient expecto-

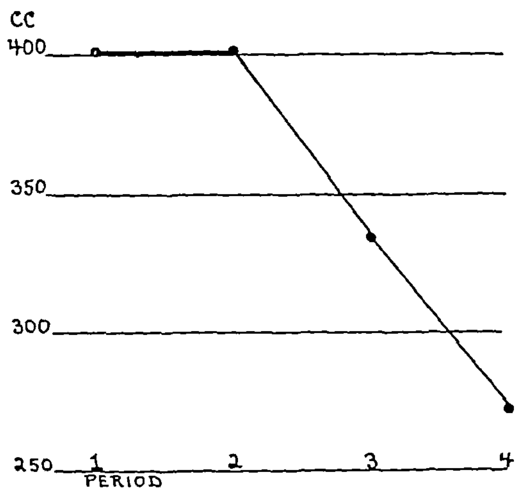

Chart 2 Sum of Secretory Volumes Shown in Chart 1

rated the mixture of bread and saliva into a large beaker in which it was thoroughly stirred up with the 500 cc of water The beaker roughly simulated the stomach immediately after in estion of the test meal In order to simulate further a constant secretion of acid into a stomach *which is emptying very slowly* 20 cc portions of N/10 HCl were added at intervals without removing any of the mixture except 10 cc samples for titration after each addition of acid

The results are shown in Chart 5, curve A It may be noted that in spite of the uniform addition of acid no free HCl (di-methyl) was demonstrated until approximately 100 cc of N/10 HCl had been introduced Thereafter there was a steady increase

Experiment 2 In this experiment conditions were identical except that moderately rapid emptying of the stomach was simulated by removing 100 cc of the test meal mixture before each addition of 20 cc of acid Chart 5, curve B, shows that in this case a "free HCl" value of 37 was reached at a point where in the previous experiment free HCl was just beginning to appear

TABLE 2

Titratable acidity at ten minute intervals after alcohol test meal

Case number	Diagnosis	Fasting	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes	60 minutes	70 minutes	80 minutes
156	Gastric ulcer	94	93	95	95					
76	Duodenal ulcer	86	112	108	101	104	108	104		
34	Duodenal ulcer	75	100	103	102					
92	Normal	80	87	92	101	104	104	106		
214	Normal	78	70	68	69	63	54			
208	Haematuria	50	84	90	90	88	84			
304	Gastric ulcer	42	102	110	118	113	114			
192	Chronic myocarditis	36	81	85	96	93	94			
178	Chronic myocarditis	60	96	92	98	92	87	83	54	
180	Congenital syphilis	34	56	62	60	60				
122	Normal	30	55	59	51	56	55			
146	Psychoneurosis	24	62	57	55	45				
80	Normal	20	32	37	35	40	43	42		
174	Abdominal adhesions	20	54	62	66	66	63			
198	Normal	16	48	51	56	68	64			
106	Ateriosclerosis	14	50	41	41	35	21	20		
94	Arteriosclerosis	0	34	38	30	30	34			
182	Pleurisy	0	20	15	20	20	15			
236	Normal	0	23	20	24					
32	Gall stones	0	30	21	14	14	13			
222	Normal	0	0	9	14					
188	Gonorrheal arthritis	10	40	54	53	56				

These experiments were carried out with the reagents of the routine clinical laboratory and without attempting greater accuracy than one observes in the usual examination of test meal specimens

Similar experiments with tap water and with distilled water alone yielded analogous results except that owing to absence of the buffer effect of the test meal and saliva "free HCl" appeared sooner

It is clear, then, that the so-called curves of acid secretion plotted from specimens removed at intervals after a test meal depend not on

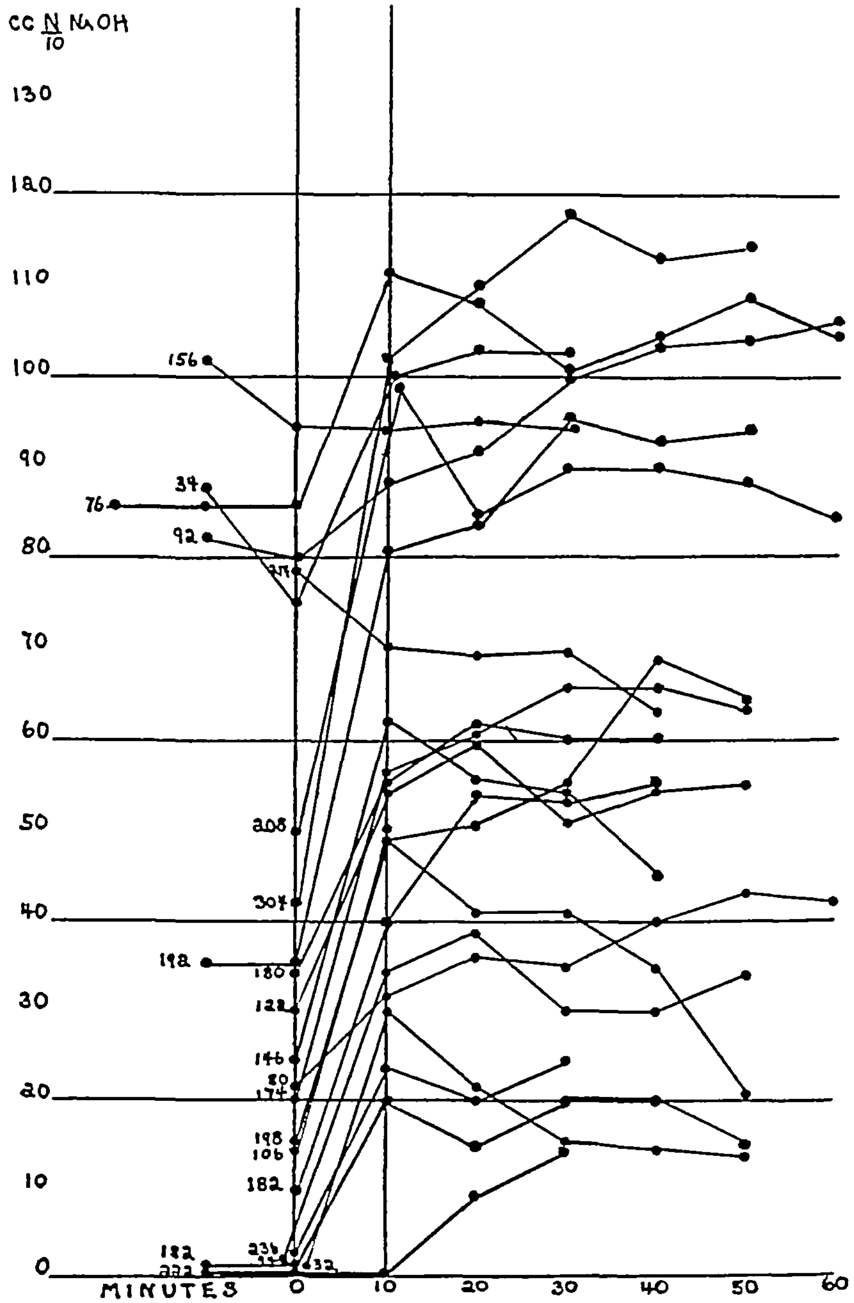

CHART 3 TITRATABLE ACIDITY OF GASTRIC JUICE AT TEN-MINUTE INTERVALS AFTER ALCOHOL MEAL

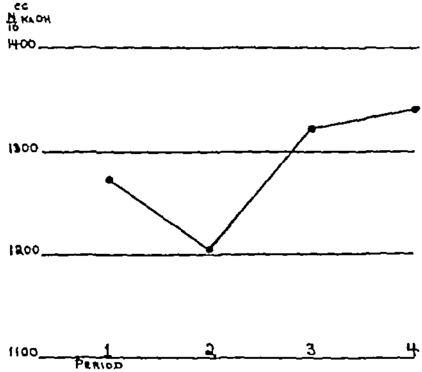

Chart 4 Composite Chart of Titratable Acidity in Cases Shown in Chart 3

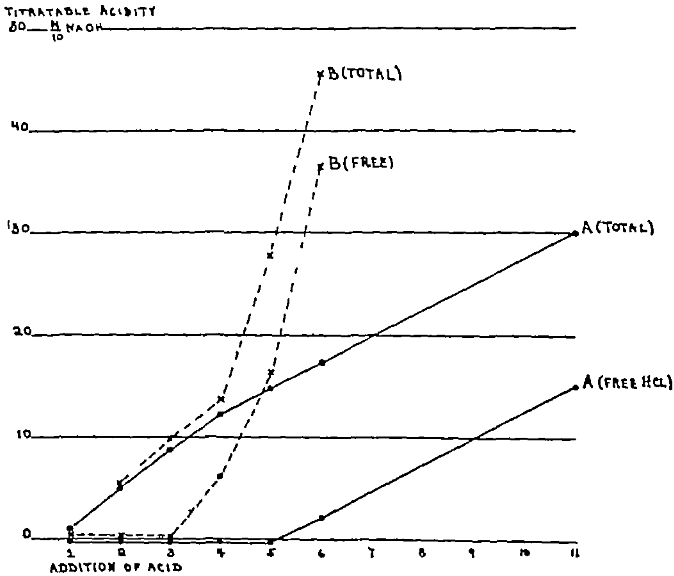

Chart 5 Artificial Test Meals—Acid Curves

the rate of acid secretion alone, but on the rate of gastric emptying as well, and an obvious explanation is furnished for the clinical instances in which on one examination no free acid is found, whereas at another time free acid is present At any rate great caution should be used in interpreting the so-called "secretory curves" after fractional meals unless the rate of emptying of the stomach is known

SUMMARY

Study of rate of gastric secretion after the alcohol test meal shows that in almost every case maximum volume of secretion and maximum degree of acidity of gastric juice is reached promptly and not gradually This finding is reconciled with the apparently contradictory "curves of acidity" obtained with fractional test meals by pointing out certain artefacts which may modify the latter

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AN ADAPTATION OF THE THERMAL CONDUCTIVITY METHOD TO THE ANALYSIS OF RESPIRATORY GASES[1]

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A simple and rapid method of analyzing respired air for carbon dioxide and oxygen is still needed in medicine In investigations on the expenditure of energy in muscular exercise, many samples of expired gas must be analyzed daily The number of such analyses has been further increased by the widespread adoption of routine clinical determinations of metabolic rates involving the respiratory exchange An improvement in the technic of obtaining such data might also be applied to studies of the composition of alveolar air and possibly to the estimation of lung volumes Accordingly it has seemed worth while to apply to the requirements of the medical profession the method of gas analysis by thermal conductivity which has proved of value along different lines to chemists and engineers

Although gas analysis by thermal conductivity was shown to be feasible as early as about 1880, it was not developed in medicine until recently and then only for the determination of carbon dioxide In 1922, A V Hill (1) reported in the Proceedings of the Physiological Society the possibilities of the "katharometer" for the rapid determination of carbon dioxide in expired air In 1926 Rabinowitch and Bazin (2) gave a more detailed account of this apparatus as produced by the Cambridge Instrument Company, and described its application for obtaining basal metabolic rates They used a "katharometer" in conjunction with a gas meter, getting in that way the data from which they calculated the metabolic rate by the method previously described by King (3) A similar apparatus, manufactured by

[1] Published by permission of Director, Bureau of Standards, Department of Commerce, Washington, D C

Siemens and Halske of Berlin, was used by Knipping (4) for the determination of carbon dioxide in alveolar airs

The "katharometer" measures the change of resistance in an unbalanced Wheatstone bridge by the deflection of the needle of a millivoltmeter In the apparatus developed by the United States Bureau of Standards,[2] which is used in the present investigation, the resistances in a Wheatstone bridge are balanced by using a slide wire to bring a galvanometer to zero deflection This type of thermal conductivity apparatus has been described by Palmer and Weaver (5), and so only a brief description will be given here

Two fine platinum wires of equal resistance, enclosed in tubes 1 cm in diameter, comprise two arms of the Wheatstone bridge, and are heated by an electric current When the wires are surrounded by gas of the same composition, heat is conducted from them through the gas at the same rate, maintaining their electrical resistances constant and equal Any change in the composition of the gas around one wire is attended by a proportional change in the quantity of heat conducted by the gas from the wire and, therefore, by a corresponding change in its temperature and electrical resistance If the composition of the gas around the second wire remains constant, the difference between two settings of the slide wire required to bring the bridge to balance, is a measure of the change in the composition of the gas which surrounds the first wire The significance of the readings can be determined only when the instrument has been calibrated for variations in the amount of one constituent in a gas mixture, the other constituents of which remain substantially constant, the instrument cannot be used for qualitative analysis in any case

DESCRIPTION

Figure 1 gives a diagram of the electrical circuit used Current is supplied by a storage battery The voltage of the circuit is kept constant by adjusting the rheostat, so that the galvanometer in the voltage-adjustment bridge is brought to zero reading One arm of this bridge is a small lamp with a tungsten filament The opposite arm

[2] The authors are greatly indebted to E R Weaver of the Bureau of Standards' staff for his advice and encouragement throughout the difficulties attending the development of this instrument

is a lamp with a carbon filament, and the remaining arms are fixed resistances of manganin wire The bridge functions by virtue of the fact that the electrical resistance of carbon decreases with rising tem-

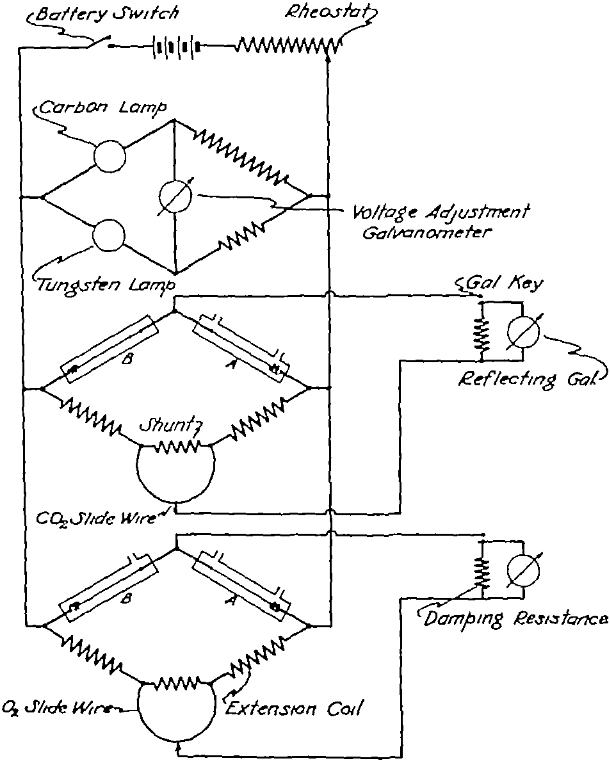

FIG 1 ADAPTATION OF THERMAL CONDUCTIVITY METHOD TO ANALYSIS OF RESPIRATORY GASES

perature, while that of tungsten increases A change of voltage will produce a corresponding change in the temperature of the lamp fila-

ments and will unbalance the bridge The voltage in the circuit can therefore be kept constant by maintaining the balance of the bridge as indicated by a moderately sensitive galvanometer

In the other two bridges, each platinum wire forming one of the arms is enclosed in a cylindrical brass cell from which the wire is properly insulated Cell A in each bridge is equipped with two metal tubes, through which passes the gas to be analyzed, thus serving

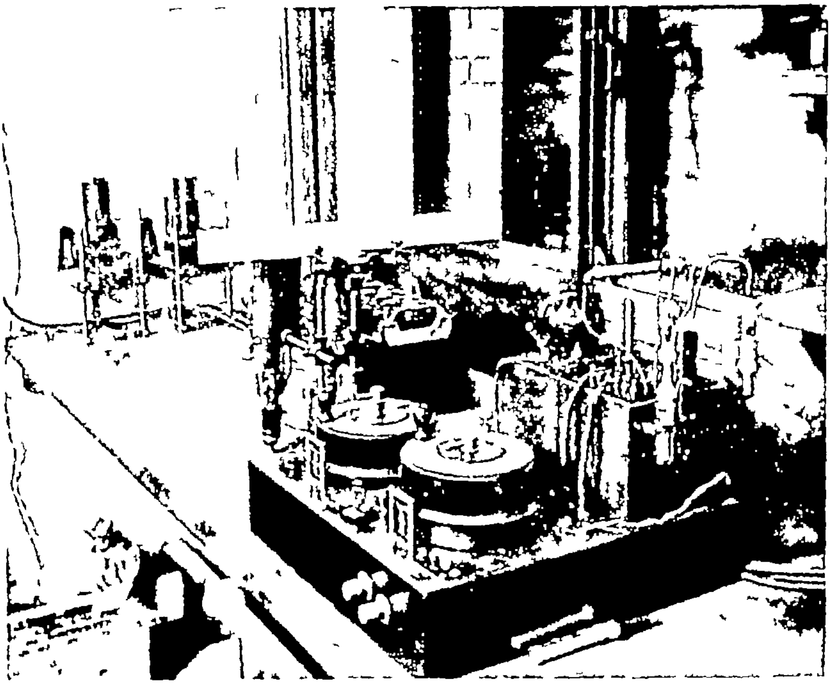

Fig 2

as the "analysis cell" Cell B is filled with gas of a constant composition (air in this case) which serves as a standard of comparison In the carbon dioxide bridge, this cell is sealed off In the oxygen bridge, where the sensitivity must be much greater, it is open to the room air through a drying tube, in order to compensate for the effect of variations in barometric pressure The other two arms of each analysis-bridge consist of the two end-coils (28 95 ohms each) and a shunted Kohlrausch slide wire The sensitivity of the bridge is de-

termined by the resistance of the shunt across the ends of the slide wire In order to make the bridge for oxygen analysis sufficiently sensitive, the resistance of its shunt is extremely low (less than one-tenth of that across the slide wire on the bridge for carbon dioxide analysis) Highly sensitive mirror galvanometers are used to indicate when these bridges are balanced

The thermal conductivity cells are kept at a constant temperature of 40°C by immersion in a small oil bath electrically stirred and heated The temperature is controlled by means of a mercury thermo-regulator To further decrease the effect of variations of temperature, the cells are enclosed in copper jackets (3.5 cm square and slightly larger than the cells) which are then filled with fine shot This volume of metal around the cells provides sufficient heat capacity to virtually eliminate all fluctuations in temperature The influence of temperature on the bridge for oxygen analysis is further minimized by keeping its end-coils in the oil bath Connections from these coils to the ends of the slide wire are made of heavy copper wire Figure 2 is a photograph of the apparatus as used in the laboratory

METHOD OF OPERATION

It has been found that 200 to 250 cc of gas will sufficiently sweep out the system and give a dependable reading with this apparatus The gas passes first through a drying tube into the analysis-cell of the carbon dioxide bridge, then through reagents which remove carbon dioxide and the water vapor which is produced during the absorption of carbon dioxide, and continues through the analysis-cell of the oxygen bridge A small bubbling tube is connected to its outlet to indicate the rate of gas flow It is possible to pass a sample through in one minute Higher rates than this do not give sufficient contact with the reagents to completely remove water and carbon dioxide The sampler is then disconnected to insure atmospheric pressure in the cells leaving them filled with the gas sample, which remains constant for some time, since diffusion to the atmosphere takes place very slowly The slide wires of both bridges are adjusted to bring the deflections of the galvanometers to zero, and the settings are read directly from the slide wire scales

The apparatus is extremely sensitive to slight changes in electrical resistance Fluctuations of room temperature and of atmospheric pressure, as well as other less important factors, produce variations in the readings obtained from the same gas at different times These sources of inaccuracy are too great to be ignored, but they are compensated for if room air, from which carbon dioxide and water vapor have been removed, is swept through before each analysis Readings on

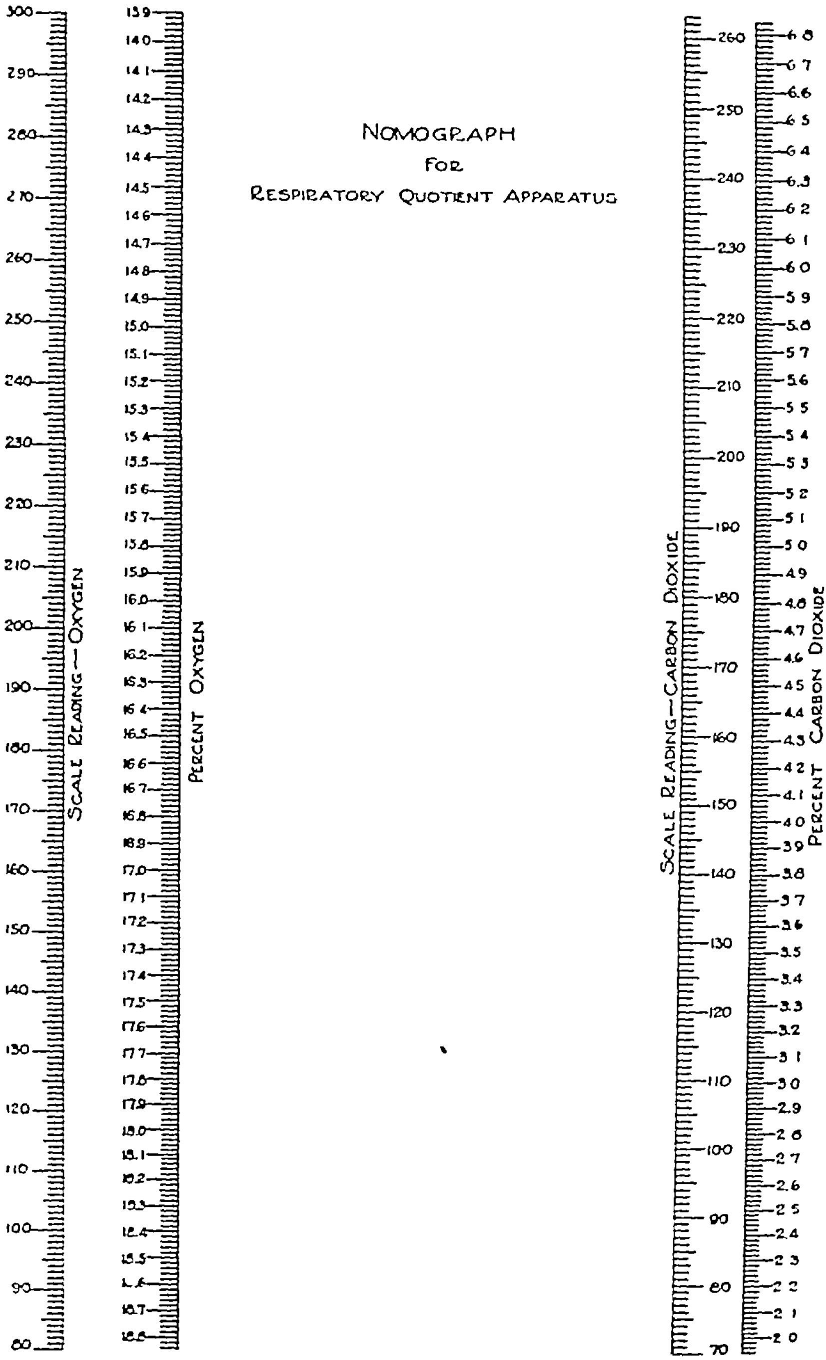
Nomograph
For
Respiratory Quotient Apparatus
Scale Reading—Oxygen
Percent Oxygen
Scale Reading—Carbon Dioxide
Percent Carbon Dioxide

Fig 3

both bridges which are taken on this air serve as "base-line" readings Differences between these readings and those obtained from the sample analyzed are the "scale readings" used in determining the results of the analysis

Two solid reagents of relatively recent introduction are used For removing water vapor Dehydrite (magnesium perchlorate trihydrate) (6) has been found the most satisfactory Ascarite (sodium hydroxide deposited on asbestos fiber) has been found the best for removing carbon dioxide Soda lime is unsatisfactory because it does not completely absorb carbon dioxide from a thoroughly dried gas

An empirical calibration of each thermal conductivity apparatus is necessary because there is no direct method of determining what the changes of electrical resistance indicated may mean in terms of gas composition It was necessary in this case to completely calibrate the apparatus against analyses of respired air made with the Haldane apparatus Scale readings were plotted against percentages obtained by the Haldane method for both oxygen and carbon dioxide The curves so produced covered the useful range of the apparatus for physiological purposes, which is about two to seven per cent of carbon dioxide and fourteen to eighteen and a half per cent of oxygen From these curves a nomograph was constructed (fig 3) A straight edge laid across the scale readings as they appear on it gives directly the percentages of carbon dioxide and of oxygen. On the oxygen side of the graph a correction is incorporated which allows for the loss of gas volume on absorption of carbon dioxide before the oxygen reading is made. In addition a correction is made in the carbon dioxide scale to provide for slight changes in thermal conductivity in the carbon dioxide cell as the proportions of oxygen and nitrogen vary in the gas sample

DISCUSSION

The adoption by the medical profession of technical improvements developed in the field of physics or chemistry may be considered justified if they increase the accuracy, simplify the manipulation, decrease the cost, or shorten the time involved in obtaining the data desired Methods of gas analysis with a Haldane or Carpenter apparatus have given results of sufficient precision for the physiological applications in which they are commonly used The time required to obtain duplicate analyses has however been their chief drawback. It is the rapidity with which the apparatus described in this paper operates that constitutes its main contribution to physiology and medicine—allowing more samples to be analyzed by one person than formerly was possible, or else releasing investigators for a closer study of results The actual time taken for duplicate analyses of gas samples is short One sample after another may be analyzed at a rate of about

TABLE 1

Analyses made by the thermal conductivity method and by the Haldane method are compared Analyses of respired gases made by the thermal conductivity method are used to determine respiratory quotients during a nine day dietary experiment

Date (1927)	Thermal conductivity		Haldane		Respiratory quotient	
	CO_2	O_2	CO_2	O_2		
	per cent	*per cent*	*per cent*	*per cent*		
March 8	2 83	17 55	2 81	17 56	0 791	Ordinary "house diet"
	3 26	17 01	3 27	16 98	0 786	
March 9	3 12	17 18	3 14	17 16	0 786	
	3 30	17 20	3 32	17 16	0 849	
March 10	3 05	17 32	3 07	17 32	0 801	High carbohydrate diet
	3 07	17 51’	3 10	17 56	0 863	
	3 26	17 37	3 29	17 39	0 885	
March 11	3 07	17 41	3 10	17 41	0 833	High fat diet Acetone in urine in increasing amounts
	3 19	17 17	3 23	17 19	0 806	
March 12	3 02	17 28	3 02	17 27	0 781	
	3 11	16 98			0 737	
March 13	3 08	17 10	3 09	17 09	0 755	
	3 16	17 00			0 754	
March 14	3 08	17 15			0 766	
	3 02	17 19			0 759	
	2 94	17 19			0 735	
March 15	2 78	17 50			0 762	
	2 87	17 28			0 734	
	2 58	17 46			0 686	
March 16	2 75	17 29			0 699	Did not take full diet Less acetone in urine
	2 91	17 13			0 711	
	2 85	17 35			0 746	

The first set of figures on each day was obtained under the post-absorptive conditions of routine basal metabolic rate determinations The last set was taken on each day in the mid afternoon. When three sets occur, the second shows results obtained about two hours after breakfast.

one every five to seven minutes, alternating, or at least being interspersed with, "base-line" readings as described in the procedure

An automatic recorder for making a continuous curve to indicate the fluctuations in the thermal conductivity of a stream of gas flowing through such an apparatus would be desirable A recorder has, in fact, been used with "katharometers" for recording carbon dioxide concentrations only But it is impossible to apply it to the determination of oxygen with sufficient accuracy to be of value, because recording instruments of the necessary sensitivity have not yet been produced

The actual manipulation is simple There are only a few operations which enter into the process of making an analysis (1) introducing the sample, (2) bringing the galvanometer needle on the voltage adjustment bridge to zero, (3) adjusting the galvanometer reflections in the analysis-bridges by means of the slide wires, (4) reading the slide wire settings, (5) getting the differences between the base-line and the analysis readings by substraction, and (6) reading the percentages of carbon dioxide and oxygen directly from the nomograph No further calculations are necessary in using this apparatus This eliminates a possibility of error which is always present in making analyses with the Haldane method With regard to keeping the apparatus in operating condition, one need only attend to charging the battery at intervals and to changing the reagents in the drying tubes occasionally The galvanometers may require occasional adjustment and it is necessary to see that the stirring motor and temperature control of the oil bath are operating satisfactorily All of these details take less time than is necessary to keep one Haldane analyzer in good condition

The accuracy obtainable is satisfactory for all practical uses involving the respiratory exchange The first criterion of the accuracy of the method is its ability to reproduce results A gas mixture was made up at high pressure in a small steel cylinder Twenty-seven readings made on the gas from this cylinder over a period of three weeks, checked each other with a maximum deviation from the mean of 0 02 per cent for oxygen Carbon dioxide readings checked each other within 0 01 per cent In making the nomograph the calibration of this apparatus was found to fit the analyses made by the

Haldane method with a maximum difference of no more than 0 05 per cent for both gases This calibration has since been put to test by a series of metabolic rates carried out on a patient before and after being put on a high-fat diet, as shown in table 1 All check analyses made by the Haldane method came within 0 05 per cent of each other and of those made by the thermal conductivity method There is no reason to assume that the failure of the two apparatuses to check each other perfectly was caused by errors of the thermal conductivity apparatus It is equally possible that the errors may have been made in individual cases by the Haldane method

The advantages of the new method of analyzing respiratory gases are accompanied by a few definite limitations Of these, probably the most serious is the cost of the sensitive and specialized equipment Only certain institutions will have occasion to purchase this type of apparatus, both because of its cost and because in them alone would the demand for air analyses warrant its use A further disadvantage is the necessity for a complete recalibration in case of damage to one or more of the thermal conductivity cells by accident or excessive current This might put the apparatus out of use for some time The size of the gas sample needed to sweep out the system may in some cases also limit the field to which this apparatus can be applied Although this difficulty has not been investigated, it is barely possible that in certain pathological conditions the expired air may contain gases or-vapors (such as acetone in diabetes) which would not affect the analysis made by the Haldane apparatus, but which might slightly shift the thermal conductivity readings And finally, in case of repairs, the services of a skilled worker familiar with electrical measurements would be essential

SUMMARY

1 An apparatus has been developed for the analysis by thermal conductivity of both carbon dioxide and oxygen in respiratory gases

2 The principles of construction and method of operation are described

3 Its potential value to medical science depends upon (a) Saving of time, duplicate analyses may be completed in ten minutes (b) simplicity of operation, (c) virtual elimination of calculation, (d) requisite accuracy

4 The only limitations which appear significant are (a) Cost of construction, (b) necessity for complete recalibration in case of accident.

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STUDIES IN EXPERIMENTAL ANEMIA

I The Effects on Rabbits of the Injection of the Hemolytic Toxin of the Welch Bacillus

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In this study the genesis of pernicious anemia has been investigated from several points of view The first two papers are concerned with the hypothesis that pernicious anemia is perhaps caused by an intoxication arising in the intestinal canal Experimental anemia was produced in the first instance by the hemolytic toxin of the Welch bacillus and in the second by the use of stool extracts from pernicious anemia patients and from normal individuals The third paper is concerned with immunologic differences between pernicious anemia and anemia due to the Welch bacillus toxin In a fourth paper experiments will be reported dealing with a change in atmospheric environment in which rabbits were exposed to three times the normal oxygen concentration in the inspired air

HISTORY

During the past twenty five years there has been presented a good deal of evidence pointing to the intestinal origin of pernicious anemia Hunter (1) (1903) first definitely advanced the theory that pernicious anemia was due to a chronic infection of the gastro-intestinal tract, believing that this view was indicated by the specific glossitis, the gastric achylia and the intestinal symptoms characteristic of the disease Kulbs (2), discovering that the intestinal contents of patients with chronic intestinal disorders contained hemolytic substances, believed the disease to be associated with hemolytic products of intestinal putrefaction Herter (3) found that the stools of pernicious anemia patients contained greatly increased numbers of B Welchii

and first suggested a relation between this organism and the genesis of pernicious anemia The findings of Herter were confirmed by Simmonds (4) and recently by Moench, Kahn and Torrey (5)[1] In 1917 Bull and Pritchett (6) showed that B Welchii elaborated a true hemolytic toxin Intravenous injection of broth cultures into rabbits was attended by severe anemia and death Intramuscular injection of like doses, however, caused death with equal certainty but without blood destruction They were able in addition to produce an antitoxin which conferred immunity to the effects of the hemolytic toxin Cornell (7) showed that rabbits infected with B Welchii developed anemia of varying degree, characterized chiefly by anisocytosis The color index showed irregular variations In the presence of definite anemia it was less often below than at or above 1 The greatest depression of blood count occurred early in the disease and was always followed by a compensatory rise which the author interpreted as the response of a healthy hemopoietic system By injecting the toxin of the Welch bacillus into monkeys Kahn and Torrey (8) produced anemia with a blood picture similar to that of pernicious anemia The color index was increased above 1 0 Poikilocytosis and macrocytosis were of moderate degree, anisocytosis was marked The anemia cleared up in about twenty days and was not reinduced by continued injection Patterson and Kast (9) found anemia of the secondary type after injection of the Welch bacillus and the toxin into rabbits It is of interest that Sapinoso, Berg and Jobling (10) found that repeated injections of distilled water caused a 40 to 50 per cent drop in the number of erythrocytes and a corresponding fall in hemoglobin There was a slight to a moderate polychromatophilia and anisocytosis with occasional normoblasts However, despite continued repeated injections, the blood count returned approximately to the normal figures present before injection

[1] Since this paper was submitted Nye reports that the same increase in B Welchii spores occurring in pernicious anemia is found in cases of gastric achylia without pernicious anemia On the basis of his observations and the tendency of B Welchii to form spores in alkaline media, be believes that the spore increase in pernicious anemia is secondary to the gastric achylia rather than indicative that pernicious anemia is caused by chronic intestinal infection with B Welchii (Nye, R N, J Clin Invest, 1927, iv, 71 Investigation Relative to B Welchii Infection of the Intestinal Tract as the Etiological Factor in Pernicious Anemia)

Faber (11) has long been interested in the conception that pernicious anemia may arise from pathological disturbances in the intestinal tract In 1895 he observed a case in which marked strictures of the small intestine were found at the postmortem examination Meulengracht (12) reported a case of a woman 64 years of age who suffered from three strictures in a segment of the small intestine and in whom the signs and symtoms of pernicious anemia made their appearance Similar observations have been made by others (Wallis, W J Mayo, Warfuringe, Ketz, P F Holts, Barker and Hunder, Schmidt, Tallquist) Faber refers the etiologic connection to resorption of hemotoxins of bacterial origin from the dilated section of intestine above the stricture These results have apparently received experimental confirmation by the work of Seyderhelm (13) In two of ten dogs in whom circular strictures of the intestines were produced a progressive hyperchromic anemia of the pernicious anemia type was produced In ten patients with pernicious anemia a preternatural anus was produced by an opening into the small intestine from which flowed a dark brown fecal fluid that could not be distinguished in appearance, odor or bacterial content from large intestinal stools In those cases in which the small intestine fistula stool changed to its normal character, i e, light color, absence of foul odor, no bacteria, there was a rapid improvement in anemia With a special technique described below he made extracts of stools of pernicious anemia patients and normal individuals, both of which produced anemia of the pernicious type when injected into rabbits Recently Dixon, Burns and Giffen (14) reported favorable results from ileostomy in patients with pernicious anemia Autor (15) reported experiments in rabbits in which extracts of the entire bacterial flora of the stools of pernicious anemia patients and extracts of B coli cultures from the same stools were repeatedly injected The injections of the mixed bacterial extracts caused no changes in the blood picture, the B coli extracts caused some anemia in a few of the animals which was not of the pernicious type

Such reports as these appeared to justify a tentative hypothesis that a hemolytic substance is formed in and absorbed from the intestinal tract of patients with pernicious anemia The nature of the substance is entirely unknown The experiments reported in this

first paper deal with the administration of the hemolytic toxin of the Welch bacillus The toxin has been given in various ways to rabbits over longer periods of time than have hitherto been employed

It is evident from the work just cited that the hemolysin can constitute only one factor in the etiology of the disease Only certain patients with stricture of the intestine develop pernicious anemia In the various dog and rabbit experiments great variation in the frequency and severity of anemia occurred Furthermore, in the Bothriocephalus type of pernicious anemia there is no question that the disease is due to the presence of the parasite, for expulsion of the worm is followed by recovery Nevertheless, in Finland it is estimated that 10 to 20 per cent of the population are infected with Bothriocephalus, although according to Schaumann's (16) experience only a few per thousand get pernicious anemia Clearly then, whatever the extrinsic hemolytic factor may be, an equally specific intrinsic individual constitutional factor must likewise be sought to explain the occurrence of the disease in some individuals and animals and not in others Draper (17) in analyzing the constitutional types of various disease groups has come to the conclusion that pernicious anemia patients have not only distinctive physical traits but also a uniformly characteristic psychic pattern From these observations he has developed the hypothesis that the pernicious anemia race represents an approach to the neutre or species type in which there has been an arrest of differentiation in psyche and soma One could imagine that there might be a different penetrability of the walls of the intestine or a peculiar genetic fault in the bone marrow of such people which represent inner counterparts of those other observable differences

We have attempted to devise experiments to test differences in constitutional reaction but the complexity and perhaps also biological fixity of the fully developed animal is such as to make this procedure difficult or impossible A number of experiments were conducted in which normal and castrate rabbits were subjected to various hemolytic agents, such as the Welch bacillus toxin and hemolytic stool extracts No differences could be observed between the castrate and the normal rabbits, these experiments were temporarily abandoned in favor of a more detailed investigation of the hemolytic agents on normal animals In the fourth paper an attempt to produce an al-

tered constitutional reaction by changing the atmospheric environment will be reported Up to the present time little work has been done from the point of view of increasing or decreasing an animal's susceptibility to disease by altering its individual constitution Indeed, this may only be possible by breeding experiments or by insults to germ plasm or embryo The obstacles to such investigations are obviously great but it is to be hoped that further interest will result in successful efforts in this direction

The mere fact that such modification experiments are being suggested indicates our strong suspicion that the rabbits may represent a type of animal which is by nature incapable of developing pernicious anemia This suspicion is of the same sort as that which is now well re established, namely, that the constitution of the patient is as much an etiologic factor of his malady as the attacking force Consequently, methods employed to change an unsusceptible constitution of that sort into a susceptible one, would be analagous, so far as its relationship to disease is concerned, to any device which might be used to shift the character or angle of impact of an external agent of disease

METHODS

The isolation and cultivation of the Welch bacillus and the preparation of its toxin were carried out according to the standard methods described by previous workers In some instances the organism was isolated by injecting a fecal suspension into the ear vein of a rabbit which was then killed, and the carcass allowed to remain at room temperature overnight The heart's blood or the liver generally contained the organism in pure culture In other instances a fecal suspension was placed in litmus milk which was then exposed to 60°C for one hour and incubated at 37° for 24 hours The organism once identified by its morphologic characteristics and its cultural reaction to growth in milk was grown in 1 per cent glucose muscle broth as made by Bull and Pritchett (6) or in veal broth (de Kruif (18)) The toxin was prepared by filtering the culture through a Berkefeldt filter Its hemolytic titre was tested by mixing graded amounts of toxin with 1 0 cc of a 5 per cent suspension of washed rabbit red blood cells

Complete hemolysis of a 5 per cent suspension of red blood cells was usually produced by 0 1 cc. of toxin and slight hemolysis as low as 0 025 cc. The hemolytic activity varied greatly, however, in individual strains of Welch bacilli As observed by Moench, Kahn and Torrey (5), strains from pernicious anemia patients were not necessarily more hemolytic than those isolated from normal individuals

The deterioration of the hemolysin was progressive and rapid at room temperature, and to a less extent when kept in the ice box It was adjusted to a pH of 7 2 and a salt concentration of 0 85 per cent Recent work by Neill (19) has explained the inactivation of B welchii hemolysin as an oxidation process He has been able to reactivate the oxidized lysin by reducing agents such as sodium hydrosulphite By this method it might be possible to keep the toxin at a standard hemolytic titre for long periods, or as he suggested by keeping small amounts of the toxin in sealed tubes In our experiments the hemolytic power of the toxin was subject to considerable variation as deterioration occurred However, we attempted to use the toxin that approximated the standard of titre given above

The hemoglobin determinations were made in the beginning with the Sahli method and later with the Dare hemoglobinometer In both instances the standards were checked from time to time with the oxygen capacity method of Van Slyke and Stadie (20)

For anaerobic culture the Novy jar with displacement of the air by hydrogen was generally used At other times a heavy seal with melted vaseline was employed

The pathological material was stained with hemotoxylin and eosin The liver was additionally stained for hemosiderin, and the spinal cord with the scarlet red fat stain

RESULTS

The blood picture of four control rabbits was studied for periods of six months to two years The red blood count and hemoglobin were measured at intervals of one to four weeks during these periods The charts of two of these rabbits are given In the first (chart 1) 19 determinations were made in eight months The red blood count was 5,500,000, the hemoglobin 80 per cent and the color index 0 73 for the greater part of this time The individual variations which occurred between counts varied from 5 to 10 per cent of the mean figure In the second (chart 2) 46 determinations were made in twenty-four months As an approximate mean the red blood count may be taken as 5,300,000, the hemoglobin as 73 per cent and the color index as 0 69 In both cases there is tendency of the red blood count and hemoglobin to increase, and in the second there is a 10 per cent increase in the color index In the second case larger variations in red blood count, hemoglobin, and color index have occurred than in any other normal in the series Variations between successive determinations of 10 per cent are frequent, and 15 per cent not uncommon Many factors are known which influence the red blood count and hemoglobin, such as

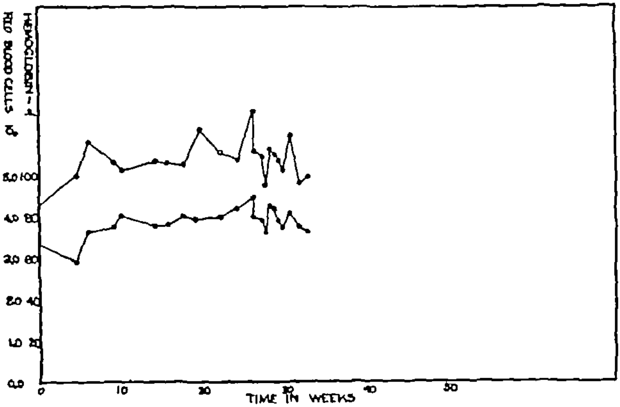

Chart 1 Red Blood Cells and Hemoglobin of a Normal Rabbit
Upper graph—red blood cells, lower graph—hemoglobin

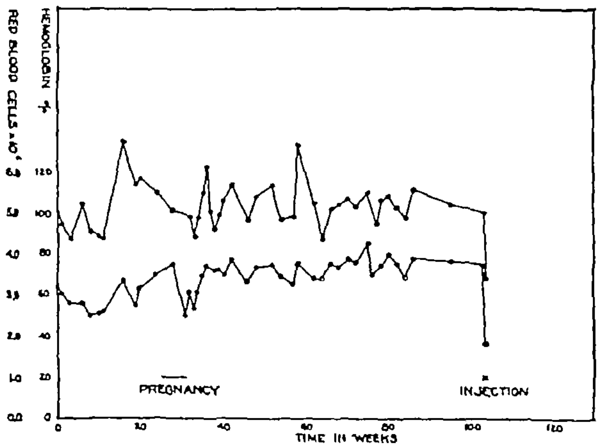

Chart 2 Red Blood Cells and Hemoglobin of a Normal Rabbit Which after a Control Period of Two Years Received Two Intravenous Injections of Welch Bacillus Toxin
Upper graph—red blood cells lower graph—hemoglobin

excitement, time of day and relation to food As far as possible the extraneous influence of these factors have been avoided in both the control and experimental animals Such variations as do occur must be recognized and considered in connection with the experimental results It is to be noted that the first rabbit had already attained adult life as indicated by a fairly constant weight, whereas the second rabbit underwent a progressive gain in weight as he became adult This fact is probably to some extent an explanation of the greater variability in blood count of the latter animal A fall in red blood

TABLE 1

Experiment 1 Anemia following single intravenous injection of Welch bacillus toxin

Date	Red blood cells	Hemoglobin	Color index	Remarks
	millions per cm	*per cent*		
August 14, 1925	4 61	63	0 68*	Blood smear normal
October 3, 1925	4 74	62	0 65†	
October 31, 1925	4 48	63	0 70	
November 11, 1925	4 40	63	0 71	
November 13, 1925	3 39	40	0 59	Marked anisocytosis, slight polychromatophilia
November 14, 1925	2 24	27	0 60	Marked aniso-, moderate poikilo-, and slight macrocytosis Marked polychromatophilia
November 16, 1925	2 24	29	0 65	Died November 17, 1925

* One cubic centimeter Welch bacillus toxin injected intravenously on November 13, 1925 Blood count recorded 3 hours later

† White blood cells rose from 7 400 to 37 800 on the following day

cells and hemoglobin maximal during the thirty-second week of observation coincided with the termination of pregnancy At the end of the control period of two years the rabbit received two intravenous injections of Welch bacillus toxin on successive days The red blood cells dropped to 2,900,000, the hemoglobin to 36 per cent The animal died on the day of the second injection

Twenty-seven experiments were performed with Welch bacillus toxin The toxin was injected intravenously, subcutaneously, intraperitoneally, and by a combination of these methods Out of this

number eight will be chosen to exemplify the various types of response Since the others were in the main confirmatory and because the data require so much space to publish, it seems best not to include them all in this report

Experiment 1 (table 1) One cubic centimeter of B Welchii toxin was injected into ear vein of rabbit Three hours later the red blood count dropped from 4 40 million to 3 39, on the following day to 2 24, on the day after to 2 24 The hemoglobin dropped for the same periods as follows 63, 40, 27, 29 per cent The color index changed as follows 0 71, 0 59, 0 60, 0 65 On the day after the last count the animal died The white blood cells rose from 7,400 to 37,800 the day after the injection, and receded to 18,600 on the second day after the injection Three hours after injection the blood smear showed slight polychromatophilia and marked anisocytosis, and on the following day, there was marked anisocytosis, slight poikilocytosis and polychromatophilia with numerous macrocytes No nucleated red corpuscles were seen The blood serum five minutes after injection showed the presence of hemolysis

In this experiment a single intravenous injection of B Welchii toxin initiated profound blood destruction and toxemia ending in the death of the animal The blood picture was that of a severe secondary anemia due to active intravascular hemolysis

Experiment 2 (table 2) Five cubic centimeters of Welch bacillus toxin were injected intravenously every two days for five doses, the toxin being of less hemolytic activity than that of the previous experiment The maximum drop in blood count occurred nine days after injection as follows Red blood cells from 5 41 millions to 2 78, hemoglobin from 70 to 38 per cent, color index changed from 0 65 to 0 69 (On two occasions during the anemia the color index was 0 80 and 0 82) After the last injection the blood count rose again and continued to do so until it reached its normal figure forty six days after the first injection The blood smear at the height of anemia showed moderate anisocytosis and polychromatophilia. Later, the blood smear returned to normal

This experiment indicates that non fatal doses of B Welchii toxin administered intravenously cause a secondary anemia which tends spontaneously to disappear

Experiment 3 (table 3). One-half cubic centimeter of B. Welchii toxin was injected intravenously twice a week for a period of thirty-six days. The maximum anemia occurred six days after the first injection, the red blood count dropped from 5.63 millions to 3.46, the hemoglobin from 81 to 46 per cent, and the color index from 0.72 to 0.67. Notwithstanding repeated injections the blood count twelve days after the first injection came up: red blood cells to 4.64 millions, hemoglobin to 58 per cent, color index 0.63. Seventeen days after the last injection the blood count dropped again: red blood cells 3.46 millions, hemoglobin 38 per cent, color index 0.55. During the periods of severe anemia there were marked anisocytosis and polychromatophilia and numerous macrocytes. The animal died the day after the last count.

TABLE 2

Red blood cells and hemoglobin after five intravenous injections of Welch bacillus toxin

Date	Red blood cells	Hemoglobin	Color index	Weight	Remarks
	millions per cm	*per cent*		*grams*	
January 14, 1926	6.08	75	0.62		Blood smear normal
January 28, 1926	5.70	69	0.61		
February 5, 1926	6.08	81	0.67	1,600	
February 18, 1926	5.50	79	0.72		
March 9, 1926	5.41	70	0.65	1,490*	
March 11, 1926	3.74	59	0.80	1,750	Slight anisocytosis and polychromatophilia
March 18, 1926	2.78	38	0.69		Moderate anisocytosis and polychromatophilia. Few macrocytes
March 24, 1926	3.90	64	0.82	†	
March 26, 1926	4.64	65	0.71		Slight anisocytosis
March 29, 1926	4.80	64	0.67		
April 6, 1926	5.22	67	0.64	1,850	
April 24, 1926	5.40	77	0.70	1,775	Smear normal
May 11, 1926	5.15	77	0.75	1,975	Smear normal

* Five cubic centimeter Welch bacillus toxin injected intravenously every 2 days.

† Injections stopped March 19, 1926.

A fairly severe anemia was produced from which the animal partially recovered notwithstanding repeated injections of toxin. However, twenty days after the last injection death occurred attended with a recurrence of severe anemia of the secondary type.

Experiment 4 (chart 3) In this experiment the rabbit was immunized by four subcutaneous injections of B Welchii toxin, 3 0 cc being given at the first dose, 5 0 cc seven days later, and two 5 cc doses at ten-day intervals Two months later 5 0 cc of toxin were administered subcutaneously three times a week for a subsequent period of fifty-two days without the development of anemia Seven months after immunization 10 cc. of toxin were administered intraperitoneally three times a week for one month without the development of definite

TABLE 3

Anemia following intravenous injection of Welch bacillus toxin

Date	Red blood cells	Hemoglobin	Color Index	Remarks
	millions per cm.	*per cent*		
November 25 1925	5 63	81	72	Smear normal
December 3, 1925	3 46	46	67*	
December 4 1925	3 68	50	74	Marked anisocytosis, polychromatophilia, and numerous macrocytes
December 9 1925	4 64	58	63	
December 15 1925	4 90	54	56	Slight anisocytosis
December 18, 1925	4 83	51	53	Slight anisocytosis
December 21, 1925	4 67	61	66	
December 30 1925	4 64	58	63	
January 6, 1926	5 47	60	55	
January 8 1926	4 90	60	62	
January 12, 1926	4 93	53	54	Slight anisocytosis
January 15 1926	3 94	50	63	Marked anisocytosis, slight poikilocytosis and polychromatophilia
January 19 1926	3 46	38	55	Same. Died January 20 1926

anemia Eight months after immunization 15 cc of toxin were administered intraperitoneally three times a week for seven weeks After a free interval of two weeks 10 cc of toxin were administered intraperitoneally three times a week for six weeks, after a free interval of ten weeks 25 cc toxin were administered intraperitoneally five times a week for five weeks During the last two weeks of this course of injections the blood count gradually dropped, the red blood cells falling to 3 64 millions and the hemoglobin to 40 per cent with a color

index of 0 55 He then received two intravenous injections of 10 cc each, and died after the last one without a final count being made

In this experiment a rabbit was immunized by four small subcutaneous injections of Welch bacillus toxin Thereafter for a period of over one year moderately large doses of Welch bacillus toxin failed to produce anemia It appeared that each course of injections increased the animal's resistance to the toxin, for doses of toxin that readily produced anemia in normal animals were without effect in this

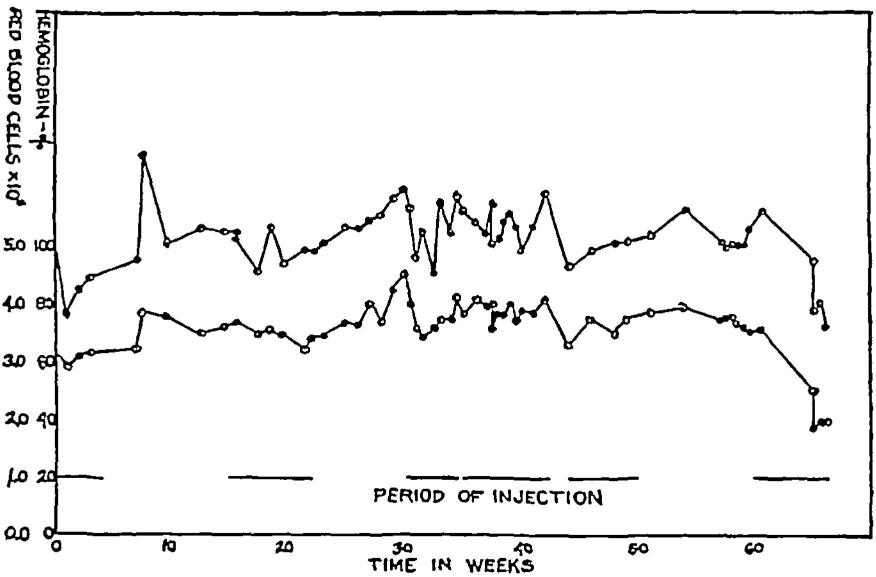

CHART 3 RED BLOOD CELLS AND HEMOGLOBIN FOLLOWING INJECTION OF WELCH BACILLUS TOXIN TO RABBIT PREVIOUSLY IMMUNIZED

Upper graph—red blood cells, lower graph—hemoglobin

instance In the third paper it is shown that the blood serum of this rabbit had developed a strong anti-hemolysin At the end, enormous intraperitoneal injections of toxin broke through the animal's resistance, and caused anemia and death

Experiment 5 (chart 4) Five cubic centimeters of Welch bacillus toxin were injected subcutaneously into a castrated rabbit each day for four months The maximum anemia developed thirty-seven days after the first injection red blood cells dropping from 5 60 millions to 3 60, the hemoglobin from 69 to 35 per cent, the color index from 0 62 to

0 49 Notwithstanding repeated injection the blood count increased sixty-four days after the first injection to its normal value, red blood cells 5 30 million, hemoglobin 70 per cent, color index 0 66 A second period of injections of toxin in 10 cc doses intraperitoneally three times a week from the thirtieth to the forty-first week of observation resulted in no anemia A third and similar course of injections from the forty-ninth to the fifty ninth week of observation likewise caused no anemia

A fourth series of intraperitoneal injections beginning with 10 cc doses and ending with 15 cc doses three times a week from the sixty-

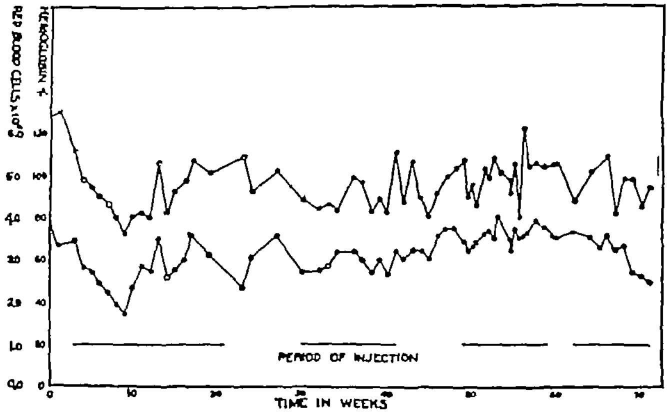

CHART 4 RED BLOOD CORPUSCLES AND HEMOGLOBIN FOLLOWING SUBCUTANEOUS AND INTRAPERITONEAL INJECTION OF WELCH BACILLUS TOXIN
Upper graph—red blood cells, lower graph—hemoglobin

second to the seventy first week of observation resulted in a slight fall in blood count and death of the animal Hemoglobin was 52 per cent, red blood cells 4 29 million, color index 0 68

In this experiment a secondary anemia was gradually produced by the subcutaneous injection of Welch bacillus toxin The blood count returned to normal while the injections were being continued A second and third course of injections were without effect, and a fourth caused a slight drop in the blood count As subsequent sero-

logical tests showed, the failure to produce a second severe anemia was due to the persistence of immune substances in the blood for a year following the first anemia

Experiment 6 (chart 5) Five cubic centimeters of B Welchii toxin and 2 cc of B Welchii antitoxin were mixed in a syringe and injected intravenously into a rabbit Three hours later the red blood cells dropped from 4 51 millions to 3 22, the hemoglobin from 67 to 56 per cent, and color index changed from 0 74 to 0 87 Within the next nine days four similar doses were given, the count at that time being as

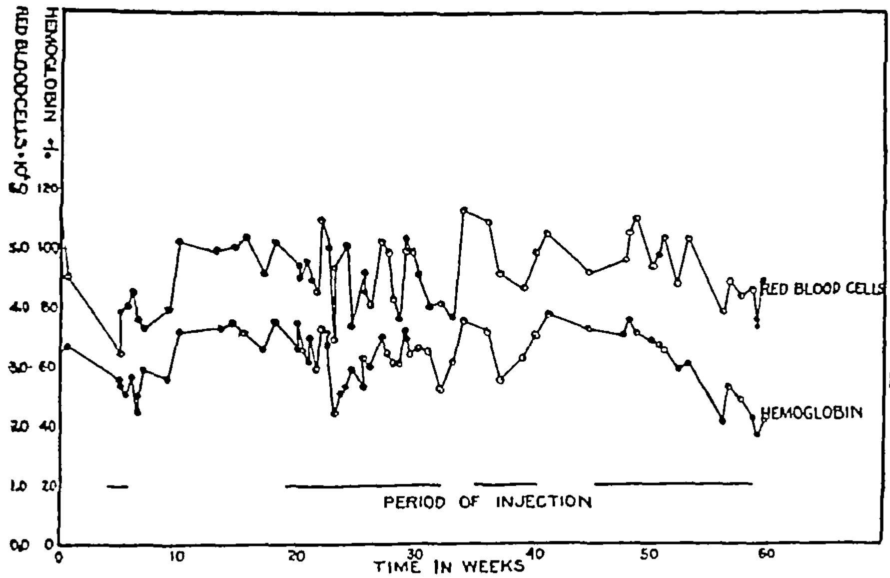

CHART 5 RED BLOOD CELLS AND HEMOGLOBIN FOLLOWING INTRAVENOUS AND INTRAPERITONEAL INJECTION OF WELCH BACILLUS TOXIN

follows red blood cells, 3 74 millions, hemoglobin 45 per cent, color index 0 61 The blood smear showed marked anisocytosis and polychromatophilia (Twenty-four days after the last injection the blood count had returned to normal) Three months later 10 cc toxin were administered intraperitoneally three times a week for six and a half weeks At the end of three weeks the red blood cells dropped to 3 46 millions, the hemoglobin to 44 per cent, the color index to 0 64, but one month later the blood count was normal After a free interval of three weeks a similar course of injections was given for five

weeks Another drop in blood count occurred followed by a return to the normal After a free interval of five weeks the same course of injection was given for seven weeks Immediately after this 25 cc of toxin were administered intraperitoneally three times a week for five weeks The rabbit then received three intravenous injections of 10 cc each on successive days, and died six days after the last injection As a result of this final series of injections the blood count gradually dropped, reaching its lowest level three days after the terminal injection, red blood cells 3 66 millions, hemoglobin 36 per cent,

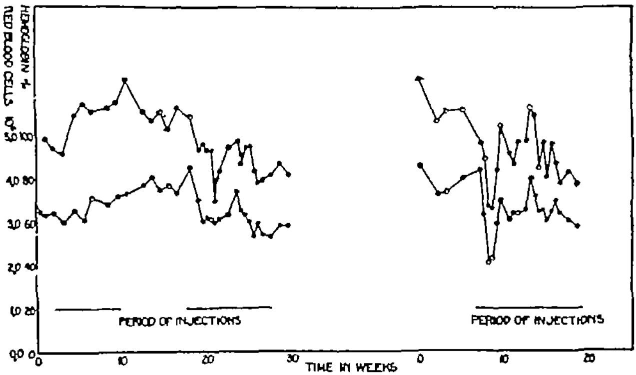

CHART 6 LEFT—RED BLOOD CORPUSCLES AND HEMOGLOBIN FOLLOWING SUBCUTANEOUS AND INTRAPERITONEAL INJECTION OF WELCH BACILLUS TOXIN RIGHT—RABBIT NO 166 SAME, FOLLOWING INTRAPERITONEAL INJECTION OF WELCH BACILLUS TOXIN

color index 0 49 The smear at the periods of anemia showed the same characteristics hitherto noted marked anisocytosis, moderate polychromatophilia, slight poikilocytosis and macrocytosis, rare nucleated red corpuscles (always normoblasts when encountered) Chart 5 shows the changes noted above in relation to the periods of injection

In this experiment carried over a period of one year four distinct periods of anemia were produced as a result of four courses of injection of Welch bacillus toxin, the first three followed by a remission

and the fourth by death of the animal During the second long course there were frequent shifts from a low to a normal count In the last course relatively large doses of toxin were needed to break down the animal's resistance The anemia was of the secondary type

Experiment 7 (chart 6) Five cubic centimeters B Welchii toxin were given subcutaneously three times a week for three weeks, and then 10 cc were administered in the same manner for three additional weeks without the development of anemia Two months later 10 cc of toxin were administered intraperitoneally three times a week for two and a half months A slight anemia began sixteen days later, red blood cells falling from 5 14 millions to 3 49, hemoglobin from 85 to 59 per cent, color index changing from 0 79 to 0 85 One and a half months later the red blood cells had risen to 4 86 millions, the hemoglobin to 74 per cent, the color index was 0 76 Three weeks afterward the count again dropped, red blood cells 3 97 millions, hemoglobin 54 per cent, color index 0 68 Anemia of this mild character persisted, and the animal died one month later

In this experiment the subcutaneous administration of Welch bacillus hemolysin failed to produce anemia whereas the intraperitoneal injection in similar doses produced a mild anemia which was maintained for the greater part of two months This experiment together with others not reported indicates that of the three methods employed the subcutaneous administration of toxin is the least effective in causing anemia

Experiment 8 (chart 6) (166) Ten cubic centimeters B Welchii toxin were injected intraperitoneally three times a week for three weeks After a free interval of one month a second course of injection was given in the same manner for four weeks The maximum anemia developed seven days after the first injection, red blood cells dropping from 5 60 millions to 3 36 millions, the hemoglobin from 80 to 41 per cent, the color index from 0 71 to 0 61 The blood smear showed slight poikilocytosis and polychromatophilia, marked anisocytosis, and numerous macrocytes Seventeen days after the first injection the red blood cells had returned to 5 22 millions, the hemoglobin to 70 per cent, the color index to 0 67 The blood count began to go down again during the second course of injections and on the last day of injection, the day before death was red blood cells 3 90 millions, hemoglobin 58 per cent, color index 0 74

In this experiment the intraperitoneal injection of toxin in two courses was responsible for the development of anemia each time, although less marked on the second occasion The first anemia occurred more promptly and with smaller doses than the second Presumably, the animal develops some immunity during the first period of injection which accounts for the difficulty of rendering him anemic the second or third time

PATHOLOGY

The sections of the bone marrow of anemic rabbits generally showed marked hyperplasia of the red cell elements The liver frequently revealed small deposits of iron The spinal cord did not show the degenerative changes associated with combined sclerosis and pernicious anemia. Other changes were irregularly observed such as leukocytic infiltration of the portal spaces of the liver, congestion of the liver or spleen, cloudy swelling and fatty degeneration of the parenchyma cells of the liver and the grey and white matter of the cord The pathological histology of the organs studied was not characteristic of pernicious anemia but appeared to be consistent with blood destruction from an active hemotoxin

DISCUSSION

Twenty-seven experiments with Welch bacillus toxin were carried out over a period of two years Rabbits were injected intravenously, subcutaneously and intraperitoneally, and by a combination of these methods Various degrees and types of anemia were produced, from a severe intravascular hemolysis fatal to the animal in three hours to a long continued remittent anemia of one year's duration

The intravenous injection of strong Welch bacillus toxin results in severe anemia which may be fatal in several hours or several days The serum gives evidence of hemolysis immediately after injection The smear is that of a hemolytic secondary anemia, with anisocytosis constantly the predominating characteristic. Polychromatophilia is usually well marked, poikilocytosis and macrocytosis slight and nucleated red cells consistently rare The color index is generally unaltered or it is lowered Only infrequently and for short intervals has an increased color index been found In the anemias that have

been of long duration and recurrent in character, the tendency has been for the color index to be decreased The same picture is produced more gradually with the intraperitoneal injection of toxin, and with more difficulty necessitating larger doses, by the subcutaneous route

When an anemia is produced and the animal survives, the blood count almost invariably returns to the normal This usually takes place within three weeks, and occurs despite the continued injection of the same or larger doses of toxin The animal evidently has now developed an increased resistence to Welch bacillus toxin If enormous doses of toxin are administered intraperitoneally or intravenously when the animal is in this state, it is possible to break through the resistance and cause a recurrence of anemia The subcutaneous administration of toxin does not produce anemia in an animal previously anemic in doses which are as large as one may conveniently employ in a rabbit The second and third recurrence of anemia is usually shorter than the first, the blood count sometimes returning to the normal in four or five days In some instances, the blood count may be made to fall progressively by the continuation of enormous doses resulting finally in death of the animal At times, shortly before death of the rabbit the blood count rises markedly and may return almost to the normal value Thus, death may be the result of a toxemia that is not associated with anemia Usually, however, there is an anemia at the end

If an animal is first immunized against Welch bacillus toxin by four small subcutaneous injections at approximately weekly intervals he is protected from good-sized doses of toxin for a year afterwards but may be made anemic by very large doses given at frequent intervals It appears probable that the mechanism is a balance between the antihemolysin in the blood and the hemolysin administered In the third paper of this series the presence of anti-hemolysin is demonstrated both in the anemic and in the non-anemic phases of poisoning from the Welch bacillus toxin As a result of this swiftly occurring immunity an anemia with remissions may be produced which superficially resembles the cycles in pernicious anemia One might speculate on the basis of these observations that the intermittent character of primary anemia might be dependent on variation in immunity on the part of the organism to an hemolytic toxin However, in regard

to the acute and chronic anemia which it is possible to produce with Welch bacillus toxin our evidence points rather toward this being a typical secondary anemia due to intravascular hemolysis

Anemia due to Welch bacillus toxin, no matter how administered or over how long a period, shows the characteristics of secondary anemia The hemoglobin is generally lowered more than the red blood cells giving a low color index The smear shows a conspicuous absence of nucleated red blood cells, of marked distortion in the shape of the cells and of a predominance of macrocytes Anisocytosis and polychromatophilia are the outstanding findings The pathological study of the bone-marrow and liver reveal such alterations as might be expected of any hemolytic agent The spinal cord, stained with hemotoxylin-eosin and with fat stains, fails to show the degenerative changes frequently met with in pernicious anemia.

SUMMARY

Various types of acute and chronic anemia have been produced in the rabbit by the intravenous, subcutaneous and intraperitoneal injection of Welch bacillus hemotoxin

The anemia tends spontaneously to disappear notwithstanding the continued injection of toxin In some animals followed over long periods of time by means of very large doses repeated recurrences of anemia may be produced which superficially resemble the cycles in pernicious anemia In other animals the blood count remains up notwithstanding a prolonged period of injection of toxin Immunity to the Welch bacillus toxin is quickly produced in the rabbit, persists over a period of one year and is broken down only by large doses of toxin administered intravenously or intraperitoneally

The character of the anemia suggests a secondary type due to intravascular hemolysis Anisocytosis and polychromatophilia are the striking changes in the smear Nucleated red blood cells and marked distortion of red blood cells are conspicuously rare Macrocytosis is not predominant although common The color index is unchanged or, more commonly, diminished The section of the bone marrow and liver reveal the changes consistent with blood destruction The spinal cord sections do not show the degenerative changes seen in combined sclerosis and pernicious anemia

The failure to produce the typical changes of pernicious anemia by the injection of Welch bacillus toxin raises the question as to whether the rabbit species is constitutionally capable of developing the disease We are only justified in saying that we have been unable to demonstrate any essential similarity between pernicious anemia and experimental Welch bacillus anemia in the rabbit

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STUDIES IN EXPERIMENTAL ANEMIA

II THE EFFECT ON RABBITS OF THE INJECTION OF STOOL EXTRACTS OF PATIENTS WITH PERNICIOUS ANEMIA AND NORMAL INDIVIDUALS

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(Received for publication May 16, 1927)

The hypothesis that a toxic hemolytic substance could be recovered from the stools of pernicious anemia patients was investigated Saline stool extracts of patients suffering from pernicious anemia and those of normal individuals were administered to rabbits by intravenous and subcutaneous injection over long periods of time Stool extracts prepared by the special technique of Seyderhelm (1) were also employed In addition, total mixed cultures grown aerobically and anaerobically from the fresh stool were fed to rabbits by mouth

METHODS

Saline extracts Stools were collected for 3 to 5 days, allowed to stand in water over night, filtered through gauze and cotton, and passed through a Berkefeld N candle The concentration of the final solution represented one part of dried stool to 30 parts of water It was adjusted to a pH 7.2 and a salt content of 0 85 per cent The final product was a clear sterile solution Tests of its hemolytic activity in vitro were variable In a few instances no hemolytic power was demonstrated by incubating 1 cc of extract with 1 cc. of a 5 per cent suspension of red blood cells for one hour In others incomplete hemolysis took place with 1 cc and with 0 5 cc of extract, occasionally with 0 25 cc. of extract

Seyderhelm's technique The freshest possible feces were well mixed with about 10 times the quantity of distilled water, the suspension brought to a weak acid reaction by the addition of a little sulphuric acid and, after the addition of a 1 to 2 cm layer of toluol, shaken for several hours It was then filtered through a folded filter and the filtrate concentrated by evaporization to about one-half its volume in a water bath at 50 to 60 degrees Alkalinization as a result of the evaporization of the volatile acids was avoided by the addition of dilute sulphuric acid.

The concentrated fluid was diluted with an equal quantity of 96 per cent alcohol, shaken for several hours and filtered through a folded filter in such a way that the filtrate flowed down the walls of the vessel into an equal amount of 96 per cent alcohol Either immediately or after a few hours a flaky precipitate was formed In order to accelerate the formation of the latter, half the volume of ether was added After standing for 24 hours, the precipitate was washed with 80 per cent alcohol The filtrate contained the greater part of the substances having a hemolytic action in vitro, fatty acids, soaps, etc The precipitate supposedly contained the anemia-producing toxic substance, which did not have a hemolytic action in vitro The precipitate was now shaken up in 200 cc of physiological salt solution, filtered through cotton or gauze The final result was a neutral-reacting solution which was preserved in the ice-box with toluol

The extract made by Seyderhelm's technique was not hemolytic in vitro The saline extracts which frequently showed traces of hemolysis in vitro were incubated with Welch bacillus antitoxin and normal rabbit and normal human serum The degree of hemolysis produced by the untreated extracts was usually diminished and at times disappeared under these circumstances, but the Welch bacillus antitoxin exerted no more effect than the normal sera

The blood counts and the pathological sections were made as noted in the previous paper

RESULTS

Twenty experiments in all were performed, 8 with saline extracts of pernicious anemia stools, 8 with similar extracts of normal stools, 2 with extracts of pernicious anemia stools according to Seyderhelm's technique and 2 with mass aerobic and anaerobic stool cultures

Results of the administration of Seyderhelm's extracts Two rabbit experiments were performed Four extracts were prepared as closely as possible to the directions of Seyderhelm, although quantitative data were not always given, such as the amount of dried weight of stool in the final solution Since intravenous injection of large amounts such as 30 cc caused death of the animal, a smaller dose was given One experiment will be reported as the other showed the same results

Experiment 1 A rabbit was injected intravenously three times a week with 10 cc of extract for a period of six weeks The blood count was taken every week for this period and for three months thereafter No sign of anemia appeared At the end of the period of administration the red blood cells changed from 5 97 million to 7 10, the hemoglobin from 72 to 90 per cent, the color index from 0 60 to 0 63 The blood smear was normal throughout

In two such experiments we were unable to induce an anemic condition in rabbits who received an intravenous injection of 10 cc. of Seyderhelm's extract three times a week for six weeks

Results of the administration of saline extracts from pernicious anemia stools

Eight rabbit experiments were performed with saline extracts of stools from pernicious anemia patients In 2 rabbits anemia was produced by the intravenous injection of extract In 3 rabbits anemia

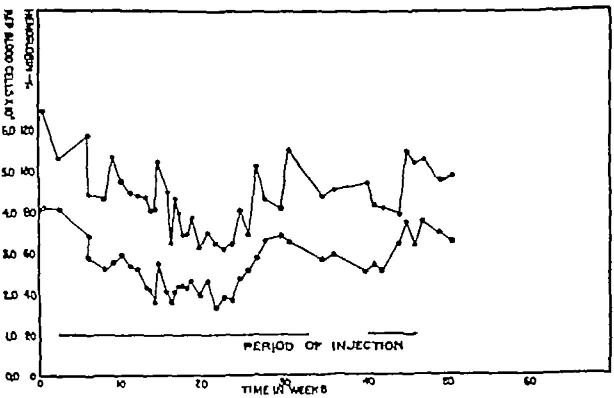

CHART 1 ANEMIA FOLLOWING SUBCUTANEOUS INJECTION OF A PERNICIOUS ANEMIA STOOL EXTRACT

Upper graph—red blood cells, lower graph—hemoglobin

was produced by long-continued subcutaneous injection In 3 rabbits the subcutaneous injection of these extracts over a similar period of time did not produce a definite anemia

Experiment 2 (chart 1) A saline extract was made from the stools of three pernicious anemia patients It was slightly hemolytic in vitro, 0.5 cc. of extract producing hemolysis of a 5 per cent suspension of red blood cells The rabbit received 4 cc subcutaneously 6 days out of 7 for eight months A severe anemia gradually developed, the

red blood cells eleven weeks after the first injection dropping from 5 30 million to 3 20, the hemoglobin from 86 to 36 per cent and the color index from 0 76 to 0 56 The blood smear at the height of the anemia showed marked anisocytosis, moderate polychromatophilia, slight poikilocytosis and numerous macrocytes Nucleated red corpuscles were absent Notwithstanding the continuance of injection, the count gradualy improved, and six months after onset of experiment had reached the following, red blood cells 5 47 millions, hemoglobin 65 per cent, color index 0 60 After a free interval of seven weeks

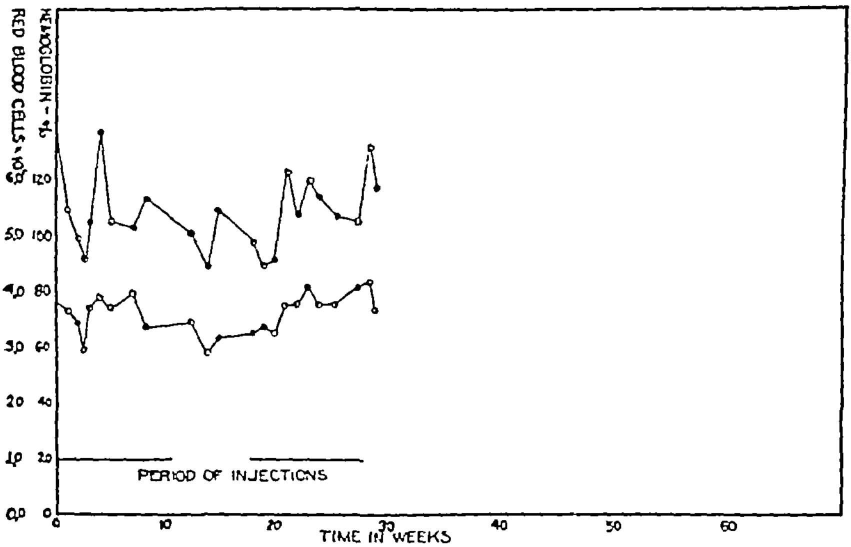

Chart 2 Red Blood Corpuscles and Hemoglobin Following Subcutaneous Injection of a Pernicious Anemia Stool Extract

Upper graph—red blood cells, lower graph—hemoglobin

10 cc of extract were administered subcutaneously 6 out of 7 days for five weeks The blood count was lowered slightly and then returned to its normal value After this course was completed, 20 cc were administered intravenously, which was followed by the death of the animal

In this experiment a severe chronic anemia was gradually produced by the long-continued subcutaneous administration of pernicious anemia stool extract In a period of one year two remissions occurred

(see chart 1) The character of the anemia resembled that due to the Welch bacillus toxin, characterized by a low color index and a blood smear of secondary anemia type In this experiment too, the blood count returned to normal during the period of injection, suggesting some immune response on the part of the organism

Experiment 3 (chart 2) Four cubic centimeters of a pernicious anemia stool extract were injected subcutaneously 6 out of 7 days for ten and a half weeks After a free interval of seven weeks, 5 cc were

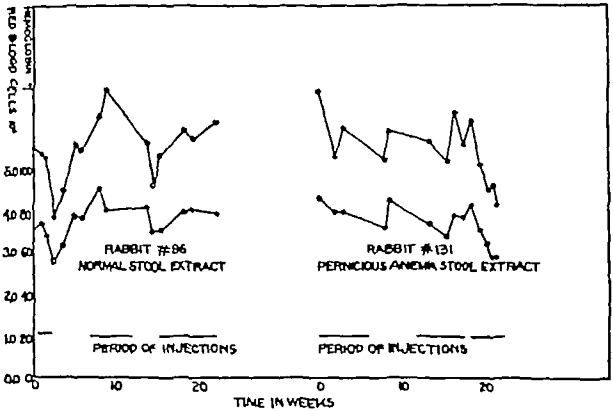

CHART 3 RED BLOOD CORPUSCLES AND HEMOGLOBIN FOLLOWING SUBCUTANEOUS AND INTRAVENOUS INJECTIONS OF STOOL EXTRACTS

Upper graphs—red blood cells, lower graphs—hemoglobin

similarly injected for ten weeks One week later 10 cc of extract were injected intravenously three times in one week, after the last of which the animal died Variations in red count and in hemoglobin occurred but no definite anemia developed (see chart 2) (This extract caused slight hemolysis when 1 cc of extract was mixed with 1 cc of a 5 per cent suspension of red blood cells)

In this instance the subcutaneous and later the intravenous injection of pernicious anemia stool extract resulted in no definite anemia

Experiment 4 (rabbit no 131) (chart 3) Five cubic centimeters

of pernicious anemia stool extract were administered subcutaneously to a rabbit 6 out of 7 days for six weeks After a free interval of six weeks the same procedure was repeated for five and a half weeks After a second free interval of one week, 10 cc of extract were intravenously injected twice a week for four weeks The day after the last injection the animal died Sixteen weeks after the onset of the experiment the blood count had dropped slightly, red blood cells from 6 94 millions to 5 22, hemoglobin from 87 to 68 per cent, color index changed from 0 63 to 0 65 Three weeks later the count went up again, red blood cells to 6 20 millions, hemoglobin 83 per cent, color index 0 65 After three weeks of intravenous injection the blood count dropped, red blood cells 4 13 millions, hemoglobin 58 per cent, color index 0 70

In this experiment a moderate reduction in red blood cells and hemoglobin occurred after subcutaneous and intravenous injection of pernicious anemia extract The color index was variable The blood smear showed anisocytosis Death occurred in this animal as in the previous one without the development of severe anemia

Results of administration of saline extracts of stools of normal individuals

Eight experiments were performed with saline extracts from the stools of normal individuals In 5 instances anemia of varying degree was produced, in 3 no anemia The extracts at times showed traces of hemolytic activity in vitro of the same degree and character as the extracts from pernicious anemia stools

Experiment 5 (chart 4) Three cubic centimeters of normal stool extract was injected subcutaneously 6 out of 7 days for twelve weeks After a free interval of eight and a half weeks 10 cc were injected subcutaneously in the same manner for four weeks During the three subsequent weeks 10 cc were intravenously administered three times a week Two days after the last injection the animal died Three weeks after the onset of the experiment the red blood cells dropped from 6 72 millions to 4 42, the hemoglobin from 77 to 64 per cent, the color index rose from 0 57 to 0 72 The blood count rose during the period of injection reaching a maximum two months later of red blood cells 5 76 millions and hemoglobin 79 per cent, color index 0 68 As a result of the intravenous injection the red blood cells dropped from 6 62

millions to 3 90, and the hemoglobin from 81 to 50 per cent The blood smear showed anisocytosis and polychromatophilia Color index was 0 64

This experiment with normal stool extract shows features similar to the results of Welch bacillus toxin and pernicious anemia stool extract A reduction in blood count may be produced by subcutaneous injections and a more severe reduction by administration through the intravenous route The anemia is temporary, notwithstanding the continuance of the injection

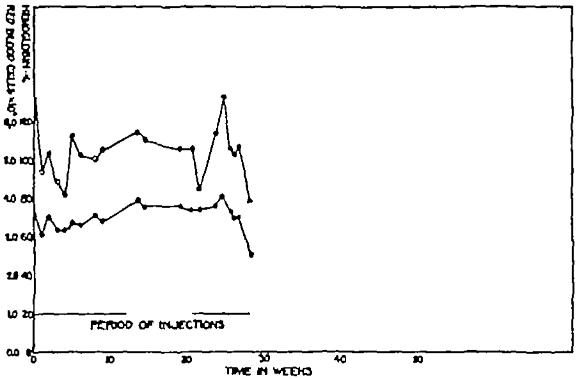

CHART 4 RED BLOOD CORPUSCLES AND HEMOGLOBIN FOLLOWING SUBCUTANEOUS INJECTION OF NORMAL STOOL EXTRACT

Upper graph—red blood cells, lower graph—hemoglobin

Experiment 6 (chart 5) Four cubic centimeters of normal stool extract were administered subcutaneously 6 out of 7 days for eleven weeks At the end of three weeks a slight reduction of red blood cells and hemoglobin occurred followed by a prompt return to the normal count (see chart) After a free interval of eleven weeks, 10 cc. of extract were administered intravenously three times a week for eleven weeks without development of anemia. Four weeks later two intraperitoneal doses of Welch bacillus toxin, 10 cc. each, were administered in three days The day after the last injection the animal died

As a result of the Welch bacillus toxin the blood count promptly dropped, red blood cells from 5 31 to 2 65 millions, the hemoglobin from 87 to 48 per cent The smear showed moderate anisocytosis and polychromatophilia Polynuclear leukocytes were much increased

In this experiment the temporary drop in blood count as a result of injection of normal stool extract, with increased resistance to subsequent injection, is again demonstrated Furthermore, when Welch bacillus toxin was later injected a severe anemia resulted in three days, indicating that the earlier hemolytic factor in the extract had not been

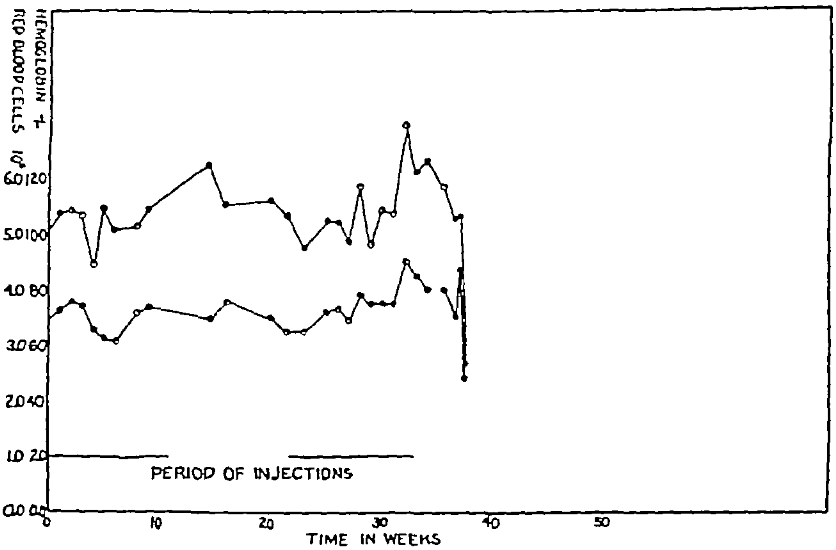

CHART 5 RED BLOOD CORPUSCLES AND HEMOGLOBIN FOLLOWING INJECTIONS OF (1) NORMAL STOOL EXTRACT, (2) WELCH BACILLUS TOXIN

Upper graph—red blood cells, lower graph—hemoglobin

Welch bacillus toxin The animal had a strong resistance to the hemolytic agent in the stool extract but none to the toxin As above referred to the anti-toxin of the Welch bacillus, did not specifically prevent the in vitro hemolysis of the normal stool extract

Experiment 7 (rabbit no 96) (chart 3) Five cubic centimeters of normal stool extract were injected intravenously into a rabbit Nine days later his blood count dropped, red blood cells from 5 36 millions to 3 81, hemoglobin from 74 to 56 per cent Smear showed slight

anisocytosis and polychromatophilia. Eighteen days later the blood count had returned to its previous level, red blood cells 5 60 millions, hemoglobin 78 per cent Smear was normal Six weeks after the first injection 5 cc of extract were administered subcutaneously 6 out of 7 days for five weeks After a free interval of one month 10 cc of extract were injected intravenously twice a week for seven weeks The animal died without the development of anemia.

In this experiment a single injection of normal stool extract intravenously resulted in a temporary anemia from which the animal soon recovered Attempts to produce anemia subsequently by subcutaneous and intravenous injection were unsuccessful Thus, following a transient anemia, resistance to the hemolytic effects of the extract appeared

Experiments 8 and 9 In these experiments mass aerobic cultures from stools of pernicious anemia patients were fed to one rabbit and mass anaerobic cultures to the second They were fed three times a week on lettuce leaves Blood counts were taken every week for six weeks No anemia developed

PATHOLOGY

The bone marrow in some cases was unaltered, in others moderate hyperplasia of the red cell elements was present The liver showed occasional small deposits of hemosiderin The spinal cord revealed no changes similar to those observed in combined sclerosis and pernicious anemia.

SUMMARY AND CONCLUSIONS

The administration of saline extracts from pernicious anemia stools to rabbits both by the subcutaneous and intravenous route sometimes results in an anemia of the secondary type The blood count is diminished generally with a lowered or stationary color index At times the color index is temporarily increased The blood smear when anemia is present is characterized mainly by anisocytosis Polychromatophilia is present, slight poikilocytosis, and slight macro cytosis but nucleated red blood cells are rare The pathological study of the bone marrow, liver and spinal cord reveals no signs characteristic of pernicious anemia

Saline extracts made from the stools of normal individuals induce the same changes as those from pernicious anemia patients

We were unable to produce anemia in rabbits by the injection of stool extracts made according to Seyderhelm's technique

The anemia caused in rabbits by extracts of pernicious anemia and normal stools shows a tendency to clear up notwithstanding the continuance of the injections The anemia may be reinduced at a later period by larger doses of extract In this respect, therefore, a similarity exists between the anemia produced by Welch bacillus toxin and that produced by stool extracts That the Welch bacillus or its toxin was not responsible for the anemia produced by the stool extracts is indicated by the fact that a rabbit injected over long periods with a normal stool extract without the development of anemia was made anemic by two injections of Welch bacillus toxin In both cases the animal develops a resistance which for the time being protects him from anemia, and in fact causes the disappearance of anemia The nature of the hemolytic substance found in stool extracts is still unknown

Our experiments show no relation between experimental anemia due to stool extracts and pernicious anemia It must be emphasized again, however, that our failure to produce pernicious anemia in rabbits may be explained as well by the possible circumstance that these animals are by nature (i e, constitutionally) unsuited to develop pernicious anemia, as by the failure to use an appropriate hemolysin

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STUDIES IN EXPERIMENTAL ANEMIA

III An Immunologic Study of the Relation between Pernicious Anemia and Anemia Due to Welch Bacillus Toxin

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With the Technical Assistance of Jacob Marcus

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(Received for publication May 16, 1927)

In the first study (1) of this series chronic anemia was produced in rabbits by the injection of Welch bacillus toxin The blood picture was characterized by (*1*) low color index, (*2*) anisocytosis without distortion of the shape of the cells, (*3*) rarity of nucleated red corpuscles The histological examination of the organs showed changes consistent with blood destruction from any cause Study of the spinal cord did not reveal the degenerative changes that are frequently found in pernicious anemia The anemia which developed, however, was characterized by remissions when the injections were continued over long periods of time The blood picture of rabbits which were given non-fatal doses returned to normal despite the continuance of injection of toxin If large doses were then given the resistance could be broken down and anemia once more produced This phenomenon could be repeated It seemed theoretically possible that the remissions in pernicious anemia were due to a varying immunity on the part of the human organism to the Welsh bacillus toxin, and that furthermore, the protoplasm of the rabbit was not suited to produce the typical changes of pernicious anemia as they occur in man For this reason it seemed important to determine the immunologic reactions associated with anemia due to Welch bacillus toxin and to compare them with those observed in pernicious anemia

Agglutination of the Welch bacillus is specific for strain Simonds (2) inoculated animals with the whole organism and observed agglutination up to 1 to 60 Agglutination in higher dilution has been

reported The sera of five patients with pernicious anemia were tested with negative results In three instances the strain derived from the stool of the patient was tested against the homologous serum Old and fresh cultures were employed, and also organisms prepared by the method of Porges The serum of rabbits made anemic by the injection of toxin, as was to be expected, also showed no agglutination

The filtrates from the above cultures were tested against the sera of five pernicious anemia patients for precipitin reaction with negative results The sera of rabbits suffering from chronic Welch bacillus anemia likewise gave no precipitin reaction with the filtrates used in producing the anemia

A study of the anti-hemotoxin furnished a method for making a comparison between the clinical and experimental anemia As shown by Bull and Pritchett (3), Welch bacillus toxin when mixed with serum containing anti-hemotoxin does not cause hemolysis in vivo Lyall (4) developed a technique for measuring the hemolytic activity of the toxin in vitro and the titre of the anti-hemotoxic serum used In this test varying amounts of toxin are incubated with 0 1 cc serum for one hour at 37°C , one cubic centimeter of a 5 per cent suspension of red blood cells is then added, and the mixture incubated for two additional hours The absence of hemolysis indicates a protective amount of anti-hemotoxin present in the serum

The toxin was prepared from veal broth made by the addition of $\frac{1}{2}$ pound of fresh veal to 1 liter of 0 2 per cent dextrose broth adjusted to a pH of 7 4 After 10 minutes boiling the pH was adjusted to 7 6 and the broth autoclaved for 15 minutes at 15 pounds pressure The broth was inoculated with a Welch bacillus isolated from a normal stool and grown under vaseline for 18 hours The culture was filtered through a Berkefeld "N" candle One cubic centimeter of a 5 per cent suspension of rabbit's red blood cells were completely hemolyzed by 0 1 cc of toxin

RESULTS

The results of these tests have been tabulated under six headings (*1*) normal human serum, (*2*) serum of patients with secondary anemia, (*3*) serum of patients with pernicious anemia, (*4*) normal rabbit serum (*5*) serum of rabbits with acute anemia due to Welch bacillus

TABLE 1

*Inhibition of hemolytic activity of Welch bacillus toxin by the serum of nine normal individuals**

Number	Amount of toxin						
	0.025 cc.	0.05 cc.	0.10 cc.	0.20 cc.	0.50 cc.	0.50 cc.	0.70 cc.
1	−	+	+++	+++	+++	+++	+++
2	−	−	+++	+++	+++	+++	+++
3	−	−	+++	+++	+++	+++	+++
4	−	−	+++	+++	+++	+++	+++
5	−	−	+++	+++	+++	+++	+++
6	−	−	+++	+++	+++	+++	+++
7	−	−	+++	+++	+++	+++	+++
8	−	−	+++	+++	+++	+++	+++
9	−	−	+++	+++	+++	+++	+++
Control	−	−	+++	+++	+++	+++	+++

* In this and subsequent tables +++ = complete hemolysis of a 5 per cent suspension of red blood cells.

TABLE 2

Inhibition of hemolytic activity of Welch bacillus toxin by serum of patients with secondary anemia

Number	Amount of toxin						
	0.025 cc.	0.05 cc.	0.10 cc.	0.20 cc.	0.30 cc.	0.50 cc.	0.70 cc.
1	−	+	+++	+++	+++	+++	+++
2	−	−	+++	+++	+++	+++	+++
Control	−	−	+++	+++	+++	+++	+++

TABLE 3

Inhibition of hemolytic activity of Welch bacillus toxin by serum of eight patients with pernicious anemia

Number	Amount of toxin						
	0.025 cc.	0.05 cc.	0.10 cc.	0.20 cc.	0.30 cc.	0.50 cc.	0.70 cc.
1	−	−	++	+++	+++	+++	+++
2	−	−	++	+++	+++	+++	+++
3	−	−	++	+++	+++	+++	+++
4	−	−	++	+++	+++	+++	+++
5	−	−	++	+++	+++	+++	+++
6	−	−	++	+++	+++	+++	+++
7	−	−	++	+++	+++	+++	+++
8	−	−	++	+++	+++	+++	+++
Control			++	+++	+++	+++	+++

toxin, (*6*) serum of rabbits with chronic anemia due to Welch bacillus toxin The cases of pernicious anemia represented various stages of the disease from the severely anemic individual to one in remission

TABLE 4

Inhibition of hemolytic activity of Welch bacillus toxin by serum of three normal rabbits

Number	Amount of toxin						
	0 025 cc.	0 05 cc.	0 10 cc.	0 20 cc.	0 30 cc.	0 50 cc.	0 70 cc
1	+	++	+++	+++	+++	+++	+++
2	–	+	+++	+++	+++	+++	+++
3	–	–	+++	+++	+++	+++	+++
Control	–	+	+++	+++	+++	+++	+++

TABLE 5

Inhibition of hemolytic activity of Welch bacillus toxin by serum of rabbits in which chronic anemia was produced by Welch bacillus toxin

Number	Amount of toxin						
	0 025 cc.	0 05 cc.	0 10 cc.	0 20 cc.	0.30 cc.	0 50 cc.	0 70 cc.
1	–	–	–	–	–	–	–
2	–	–	–	–	–	–	–
3	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–
6	–	–	–	–	–	–	–
7	–	–	–	–	–	–	–
Control	–	–	+++	+++	+++	+++	+++

TABLE 6

Inhibition of hemolytic activity of Welch bacillus toxin by serum of rabbits in which acute anemia was produced by Welch bacillus toxin

Number	Amount of toxin						
	0 025 cc.	0 05 cc.	0 10 cc.	0.20 cc.	0.30 cc.	0 50 cc.	0 70 cc.
1	–	–	+++	+++	+++	+++	+++
2	–	–	+	+	+++	+++	+++
3	–	–	++	+++	+++	+++	+++
Control	–	–	+++	+++	+++	+++	+++

In tables 1, 2, 3, and 4 are recorded respectively the results in 9 normal individuals, 2 patients with severe secondary anemia, 8 patients with pernicious anemia and 3 normal rabbits In no instance was there specific inhibition of hemolysis by any of the sera employed However, the sera of 7 rabbits in which a chronic anemia was pro duced by the repeated injection of toxin gave complete inhibition of hemolysis (table 5) In four instances two tests were made, one at the time of maximum anemia and one in remission The sera of 3 rabbits in which an acute anemia was produced by Welch bacillus toxin showed either no protection or little protection (table 6) No 1 represented a rabbit in which severe blood destruction and death resulted in four hours as a result of the intravenous injection of Welch bacillus toxin The serum gave no inhibition of hemolytic activity of toxin In no 3, the rabbit received two intravenous injections of toxin on successive days with a fall in red count from 7 0 million to 3 7 million, and of hemoglobin from 74 to 36 per cent Blood taken on the second day showed no hemolytic activity Rabbit no 2 developed an anemia of the same severity as no 3 in a period of three weeks from the intraperitoneal injection of toxin and at the end of that time his serum gave slight inhibition of hemolysis against 0 1 and 0 2 cc of toxin but none against 0 3 to 0 7 cc of toxin Later, the blood count returned to normal and the serum gave complete protection against 0 1 to 0 7 cc of toxin

SUMMARY

Interpretation of this data brings out several facts of interest The injection of Welch bacillus toxin into rabbits is followed by intravascular hemolysis which results in an anemia of varying degree depending on the amount and hemolytic titre of the toxin In three weeks after the injection of toxin the rabbit's serum contains anti hemotoxin With the appearance of anti-hemotoxin the blood count begins to return to normal Further injections of toxin are ineffective in maintaining the anemia Once the rabbit has recovered from an anemia due to Welch bacillus toxin it shows for a period of approximately one year an increased resistance to the injection of toxin The blood count remains normal with the persistence of anti-hemotoxin in the serum Large doses of toxin, however, kept up for a long period

will reinduce a severe anemia, even at a time when anti-hemotoxin is present in the blood In this way a chronic anemia has been produced with periods of remission separating the individual attacks, characterized in both phases by the presence of anti-hemotoxin

The sera of normal rabbits, normal individuals, patients with secondary anemia, and patients with pernicious anemia did not possess antihemolytic activity against Welch bacillus toxin The series of pernicious anemia patients included instances of severe anemia as well as of remission The absence of specific Welch bacillus anti-hemotoxin in the pernicious anemia patients studied and its uniform presence in chronic Welch bacillus anemia in the rabbit, suggests that these two anemias have a different etiologic mechanism.

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QUANTITATIVE PETTENKOFER VALUES IN BLOOD WITH SPECIAL REFERENCE TO HEPATIC DISEASE

A Preliminary Report[1]

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So long as there was not a satisfactory method of determining quantitatively the level of the bile acids in the blood it was practically impossible to ascertain the part these substances play in disease Since the bile acids have unusual properties and are physiologically important in the organism, it is highly desirable that something should be known of their quantitative distribution in the blood, tissues, and body fluids, and also of the changes accompanying their altered concentration With this in mind one of us (Aldrich) undertook the development of a method for the quantitative determination of bile acids in the blood The Pettenkofer reaction, although subject to several objections, appeared to offer the best basis for the method The quantitative adaptation of this reaction, is, in our opinion, of value and is yielding data of considerable significance

That bile acids may occur in the blood after biliary obstruction or intravenous injection was shown by the experiments of Kühne and Huppert Various observers have reported qualitative colorimetric tests for bile acids in the blood Moleschott, Lehmann, Blankenhorn, Gilbert Chabrol and Benard, Pétren and others obtained positive Pettenkofer tests under appropriate conditions Recently Tashiro, and Herzfeld and Haemmerli have reported partially successful attempts to adapt this test to quantitative determinations Perlzweig and Barron report a new colorimetric test for bile acids, using acetic anhydride and sulphuric acid, Szilard precipitates the bile acids with

[1] Read before the American Society of Clinical Investigation, Atlantic City, New Jersey, May 2, 1927

ferric chloride and determines the iron colorimetrically, Rosenthal and Wislicki use a modification of the gasometric method for the determination of amino-acids in the bile McNee has suggested a similar method in which the amino-acids are colorimetrically determined Because of the difficulties in the application of chemical tests, Adler and others turned to physical methods and reported extensive studies on the surface tension of serum Work which was carried on by Baldes in the laboratories of the Mayo Clinic over a period of several months led us to the conclusion that changes in the surface tension of the serum could not be used as a reliable index of the amount of bile acids present These various methods were not sensitive or specific enough, or were not clinically applicable

The quantitative Pettenkofer test which we have employed in this study is described in detail elsewhere (1) Although this test has been criticized for lack of specificity, its great sensitivity makes it particularly applicable to the analysis of blood in which the concentration of bile acids is low, and the amount of material for analysis necessarily limited Substances interfering with the specificity of the test, have, so far as possible, been removed The test requires only 5 cc of oxalated blood The bile salts are extracted from the blood with alcohol, interfering substances removed, and the Pettenkofer color developed under standard conditions, which with pure solutions of bile acids, yield results accurate within plus or minus 5 per cent The color is compared in a colorimeter, of the Duboscq type, with that developed under similar conditions by pure glycocholic acid, and results reported in terms of glycocholic acid By this method, between 90 and 100 per cent of added bile acids can be recovered

Values equivalent to from 2 5 to 6 mg of glycocholic acid have been found in normal blood, while increased values may be present in abnormal blood Care must be taken in interpreting the results obtained by a reaction which is not specific and it is not possible to attach a definite identity to all of the Pettenkofer reacting material, especially in normal blood, although as far as possible interfering substances have been removed If it is definitely accepted that bile acids are retained in the blood, as following intravenous injection, or in obstructive jaundice, the method is of value in determining the changes occurring in such conditions Since bile acids may be recovered from

the blood by this method, a normal Pettenkofer value indicates the absence of any increase of bile acids in the blood Keeping in mind such limits in interpretation of values, one may use the method to obtain information concerning the metabolism of bile acids, as shown by the changes in the content of the blood under certain experimental and clinical conditions.

PETTENKOFER VALUES IN EXPERIMENTAL STUDIES

Snell, Greene, and Rowntree have studied the level of the bile acids and bilirubin in dogs with experimental obstructive jaundice. Following ligation of the common duct, the Pettenkofer value of the blood increased gradually and, in cases in which cholecystectomy had been performed, very rapidly, often reaching the level of 30 mg for each 100 cc During experimental jaundice of long duration, both bilirubin and bile acids tended to return to normal levels, but the fluctuations in the level of the bile acids were greater than for serum bilirubin

Greene and Snell have studied the rate of elimination of bile acids from the blood stream of dogs following the intravenous injection of bile acids When the sodium salts were injected intravenously in normal dogs, the increase in the concentration in the blood was dependent on the dosage and on the rapidity of the injection In all instances, the bile salts were eliminated with extreme rapidity Even with the maximal dosage compatible with recovery of the animal (400 to 500 mg for each kilogram of body weight) the excess was eliminated within two hours In these experiments Pettenkofer values as high as 100 mg for each 100 cc of blood were attained

In other studies with this method, we elicited evidence to confirm the theory of the entero-hepatic circulation of bile acids In the fasting animal a significant difference was not found between the amounts of Pettenkofer-reacting material in the jugular and in the portal blood Within fifteen minutes after the injection of bile acids into the duodenum, increased Pettenkofer values were demonstrated in the portal blood (from 10 to 20 mg) while the values were not increased in the blood of the jugular vein An increase in the rate of bile flow and in the amount of bile acids in the bile was noted shortly after the oral administration of bile salts

Results of clinical studies Pettenkofer values in normal subjects

vary from 2 5 to 6 mg by this method These figures are based on a study of forty normal subjects (laboratory workers) and seventy hospital patients who were without evidence of hepatic disease In

TABLE 1

*Results of functional tests in various diseases of the liver**

	Cases	Bilirubin			Bromsulphthalein retention†			Bile acids		
		Minimum	Maximum	Positive	Minimum	Maximum	Positive	Minimum	Maximum	Positive
		mg per cent			*mg per cent*			*mg per cent*		
Normals										
Laboratory workers	40	0 2	1 0	0	0	2	0	2 6	5 1	0
Hospital patients	70	0 2	1 8	0	0	10	0	2 6	5 2	0
Chronic cholecystitis	40	0 2	1 9	0	0	*30*	8	3 0	5 7	0
Obstructive jaundice										
Common duct stone	14	*2 4*	*12 8*	14	*20*	*60*	14	3 4	*8 8*	6
Stricture of duct	15	1 2	*9 1*	9	*10*	*60*	15	3 7	*10 4*	2
Tumor of pancreas	8	*10 2*	*33 4*	8	*14*	*96*	8	3 0	*19 8*	5
Carcinoma										
No hepatic involvement	14	0 2	0 9	0	1	*12*	2	3 0	3 8	0
Metastasis, no jaundice	36	0 2	*5 8*	2	2	*72*	31	2 0	*8 0*	6
Metastasis and jaundice	6	*3 0*	*39 6*	6	*40*	*64*	6	4 1	*16 5*	3
Hemolytic jaundice	16	*2 9*	*8 7*		0	8		3 1	*6 2*	1
Pernicious anemia	8	0 8	*4 6*		0	8		5 3	*6 2*	1
Splenic anemia	20	0 2	*2 8*	2	0	*60*	15	3 4	*6 2*	1
Myocardial failure with passive congestion	30	0 2	*4 5*	2	8	*64*	25	2 7	5 4	0
Hypertension	16	0 2	1 7	0	0	8	0	3 2	5 7	0
Portal cirrhosis										
Small liver	16	0 6	*2 2*	3	6	*60*	14	3 9	*8 1*	2
Large liver	20	0 6	*3 1*	7	5	*64*	18	3 8	*7 2*	3
Biliary cirrhosis										
Obstructive type	11	1 2	*7 3*	7	*20*	*44*	11	2 7	*14 3*	4
Nonobstructive type	9	1 6	*17 8*	7	*24*	*56*	9	5 0	*8 0*	3

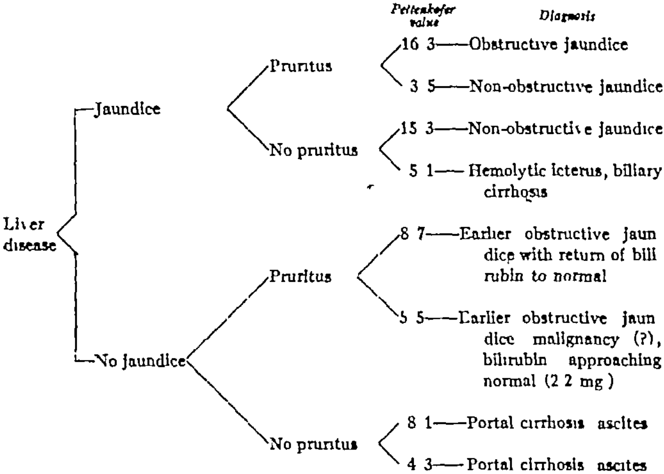
* Figures in the columns headed "positive" indicate the number of cases in the series yielding abnormal values

† Grading of sample taken at one hour

addition, between 250 and 300 patients suffering from various forms of hepatic disease were observed The highest value was 27 mg, observed in a case of fatal nonobstructive jaundice of less than two

months' duration, in which bleeding was a prominent symptom Table 1 shows the results in a series of cases, the various diseases, the minimal and maximal values for bilirubin, bromsulphalein and bile acids, together with the number of positive data with each of these tests are presented As is shown, the Pettenkofer values are not so delicate an indication of hepatic disease as are the bilirubin and dye retention tests High values are found most frequently in

CHART 1 PETTENKOFER VALUE IN RELATION TO PRURITUS AND JAUNDICE IN LIVER DISEASE



diseases associated with jaundice In general, Pettenkofer values are high early rather than late in the course of obstructive jaundice[2] As a rule practically normal values are encountered in hemolytic jaundice, pernicious anemia, splenic anemia, and in hypertension and myocardial failure with passive congestion Increased values are found occasionally in the portal and biliary types of cirrhosis

[2] This indicates that with the passage of time in cases of obstructive jaundice there is a decrease in synthesis of serum bilirubin and of bile acids For the elucidation of this problem however further studies are essential

According to the French school, bile acids are largely responsible for the pruritus and bradycardia occurring in hepatic disease, especially in jaundice Our observations thus far do not entirely con-

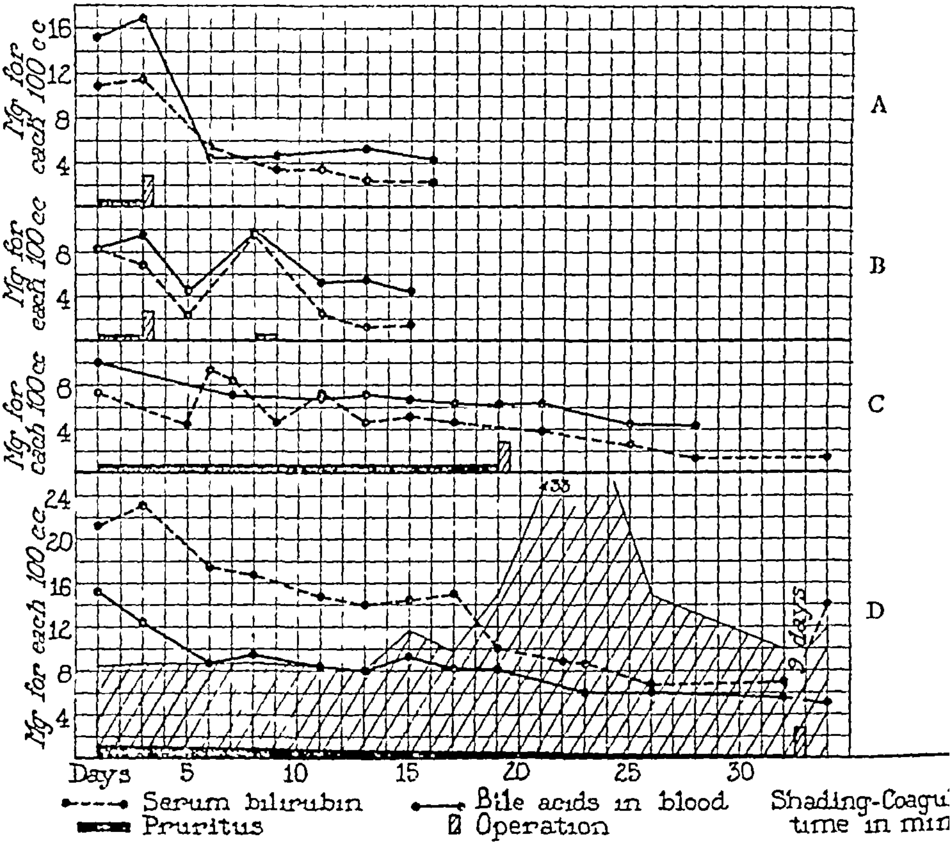


FIG 1

A Woman of 25 years *Operative diagnosis* Stricture of common duct following operation elsewhere *Operative procedure* Choledochoduodenostomy

B Woman of 62 years *Operative diagnosis* Chronic cholecystitis with cholelithiasis, pancreatitis *Operative procedure* Cholecystectomy

C Man of 70 years *Operative diagnosis* Biliary cirrhosis, suppurative cholangitis, chronic cholecystitis, pancreatitis *Operative procedure* Cholecystgastrostomy

D Woman of 43 years *Operative diagnosis* Stricture of common duct following operation elsewhere *Operative procedure* Insertion of drain

firm this view That pruritus is common in jaundice is well-known Our figures indicate that while definitely increased Pettenkofer values tend to accompany pruritus, normal Pettenkofer values may also occur

with pruritus Such observations exclude a direct causal relationship between the Pettenkofer value of the blood and pruritus This lack of relationship is further shown in the diagrammatic representation

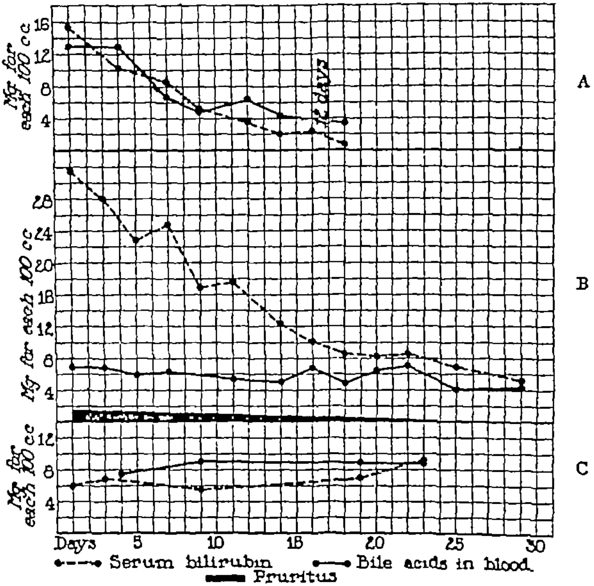


FIG. 2

A. *Catarrhal jaundice* Man aged 30 years. Three weeks painless jaundice before admission to hospital. Little or no pruritus at any time. Recovery complete at time of dismissal.

B *Catarrhal jaundice(?)* Man aged 67 years. Six weeks of jaundice and one week pruritus before admission to hospital. Edema of lower extremities developed in hospital makes diagnosis uncertain

C. *Cirrhosis of liver with splenomegaly* Man aged 31 years. Two attacks of jaundice during ten weeks preceding admission to hospital. No pruritus at any time.

of the relation of some of the signs and symptoms of hepatic disease to the acutal Pettenkofer values found in the blood (chart 1)

Disease of the liver may or may not be associated with jaundice Jaundice may be present with or without pruritus, and pruitus may

be present in the absence of jaundice High or low Pettenkofer values may be found in the presence or absence of jaundice and in the presence or absence of pruritus Neither has any relationship been established between increases in Pettenkofer values and bradycardia Bradycardia is an *infrequent accompaniment of jaundice except in the intrahepatic type* or the so-called acute catarrhal jaundice Our determinations do not appear to yield figures confirming any definite direct and causal relationship between pruritus, bradycardia and Pettenkofer values

Single determinations of bile acids by the Pettenkofer test do not appear to yield information of great diagnostic, prognostic or therapeutic value Our experience, however, is limited as yet, and more extensive study may reveal its greater significance

In utilizing functional tests for the liver, the situation is analogous to that pertaining to the kidney In the study of renal disease multiple tests are commonly employed Multiple and repeated tests also yield information of the greatest significance in the study of hepatic disease Figures 1 and 2 show in graphic form the data related to seven cases of disease of the liver Special points of interest are (1) the frequent simultaneous occurrence of high values for bile pigments and bile acids in jaundice, (2) a lack of quantitative parallelism in these two substances, although there is a decided tendency to simultaneous increase or decrease in their level in the blood, (3) striking dissociation at times in the level of bile pigments and bile acids, (4) tendency of pruritus, common in jaundice, to disappear with the relief of jaundice, and to reappear as jaundice recurs, and (5) the tendency of Pettenkofer values to increase and decrease with the appearance and disappearance of jaundice, although causal relationship between bile acid level and pruritus is not established (note curve fig 2, especially)

In the last curve decreased coagulability of the blood and hemorrhage are indicated Increased coagulation occurred during a period in which the level of the bile acids was falling and approaching normal On the other hand, uncontrollable hemorrhage has been encountered in another fatal case of nonobstructive jaundice in which the Pettenkofer values on three occasions were between 20 and 26 mg for each 100 cc of blood The addition in vitro of similar amounts of

bile salts to normal blood has only a minimal effect on its coagulation time Such relationship of bile acids to the coagulability of the blood is being investigated

SUMMARY AND CONCLUSIONS

Determinations of the quantitative Pettenkofer value in blood have been made in a study of hepatic disease Studies have been made of animals, and several hundred determinations have been carried out on patients in the wards The Pettenkofer value of normal blood varies from 2 5 to 6 mg (in terms of glycocholic acid) for each 100 cc Marked increases in these values are found in obstructive experimental jaundice, and after the injection of bile salts into the blood stream Bile salts so administered leave the circulation rapidly The administration of bile salts by mouth definitely increases their level in the portal vein but not in the peripheral circulation, and increased quantities of bile acids may be quickly recovered from the bile

Increased Pettenkofer values are frequently encountered clinically in hepatic disease High values are most common in the presence of jaundice and in the earlier rather than the later stages of obstructive jaundice High values may be found in cirrhosis of the liver in the absence of jaundice Pruritus is commonly encountered in jaundice and is frequently associated with high Pettenkofer values However, a direct causal relationship is lacking, since high values may persist over periods of weeks without pruritus, and itching in chronic disease of the liver may be marked, when the Pettenkofer value is strictly normal With high Pettenkofer values, tachycardia or normal pulse rate is encountered more frequently than is bradycardia The level of the Pettenkofer value does not seem to bear a direct causal relationship to decreased coagulability of the blood or to hemorrhage in cases of jaundice Further clinical and experimental studies relating to the amounts of bile acids in the blood and tissues, and the effects of their altered concentration on various physiologic functions, are in progress

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STUDIES ON THE VELOCITY OF BLOOD FLOW

VIII THE VELOCITY OF BLOOD FLOW AND ITS RELATION TO OTHER ASPECTS OF THE CIRCULATION IN PATIENTS WITH PULMONARY EMPHYSEMA[1]

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Pulmonary emphysema frequently presents one of the most perplexing problems of differential diagnosis in clinical medicine because the cardinal symptoms, dyspnea, cough, and cyanosis are characteristic also of circulatory insufficiency In many patients, the history and signs of cardiac pathology enable one to make a diagnosis of cardiovascular disease with confidence, but in others, with little or no evidence of heart disease and with no signs of peripheral congestion, the problem arises as to whether the dyspnea of the patient is due to early myocardial failure or to the disordered gaseous exchange of pulmonary emphysema Frequently, the problem is still further complicated by the simultaneous presence of both conditions It then becomes a matter of considerable clinical importance to estimate the relative significance of these two conditions in producing the cough, dyspnea, and lowered vital capacity, because proper treatment and accurate prognosis require such differentiation (1)

Unfortunately, our knowledge of the underlying pathological physiology of pulmonary emphysema, upon which rational diagnosis and therapeutics must be based, is incomplete Studies on the circulation in patients suffering from pulmonary emphysema are especially lacking since direct measurement of the blood flow through the lungs has hitherto been impossible, and because other data on

[1] This study was aided by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases, and from the De Lamar Mobile Research Fund of Harvard University

the circulation in emphysema are scanty Our understanding has been based, therefore, mainly on experiments on animals, on clinical observations, and on post mortem findings The possibility of obtaining information of the rôle of circulatory failure in emphysema is considerably enhanced by direct measurements of the velocity of blood flow according to a method which has recently been devised

RÉSUMÉ OF LITERATURE ON THE INFLUENCE OF MECHANICAL FACTORS IN ALTERING BLOOD FLOW IN PULMONARY EMPHYSEMA

The factors which may influence the circulation in emphysema may be classified into four groups according to Fraenkel (2) and Stähelin (3) (1) increased inspiratory position of the lungs, (2) increased intra-alveolar pressure, (3) obliteration of the pulmonary capillaries, (4) alterations in rate and depth of respiration Since the first and fourth points are closely related, they will be discussed together

1 and 4 The influence of distention of the lungs and of alterations in rate and depth of respiratory movements on the pulmonary circulation

The effect of distention of the lungs on pulmonary blood flow has interested both physiologists and clinicians for a long time Although considerable work has been accomplished, the effect of increased expansion of the lung on the pulmonary circulation is not definitely established In 1903, Tigerstedt (4), reviewing the available data, concluded that the blood flow through the lungs increases during inspiration Similarly, Lohmann and Müller (5), in 1913, experimenting on excised lung tissue, concluded that distention of the lungs permitted increased blood flow Cloetta (6), on the basis of experiments on animals and later observations on models of pulmonary vessels, concluded that there is no essential change in blood flow during normal inspiration In pathological respiration, however, such as in shallow, rapid breathing, the blood flow is increased, while with slow and deep respiration, such as may occur in emphysema, there is a decrease in blood flow

The relationship between pulmonary ventilation and the minute volume output of the heart in dogs was studied recently by Marshall (8) He found no changes in the minute volume output of the heart when the ventilation showed a change of 100 per cent or more Similarly, Drinker, Churchill, and Ferry (9) found "little variation in pulmonary blood volume under different conditions of the respiration"

In a considerable number of patients suffering from emphysema respiratory movements are rather deep, because the increase in rate is not proportional to the increase in minute volume of respiration Stähelin and Schutze (10) found the total minute volume of the respiration averaged 10 1 liters in patients suffering from emphysema, in contrast to 7 6 liters in normal subjects

2 *The effect of increased intra-alveolar pressure*

The intra-alveolar pressure may become abnormally high during expiration with narrowing of the small bronchioles, as in bronchial asthma and bronchitis, or with forceful and short expiration, as in cough. Such increased intrathoracic pressure may embarrass pulmonary blood flow considerably V Rohden (11) has shown experimentally that the capacity of the pulmonary capillaries is directly influenced by the intra alveolar pressure With increase in the intra-pulmonary pressure he observed a decrease in the pulmonary blood flow If pulmonary emphysema is associated with bronchial asthma, or chronic bronchitis, it is probable that intra pulmonary pressure is, at least temporarily, high The significance of this factor has received considerable theoretical consideration by a number of clinicians in the past

3 *The effect of obliteration of the capillaries of the lungs on the pulmonary circulation*

Whether, as a result of atrophy and rupture of alveoli, sufficient obliteration of the pulmonary capillaries occurs to cause increased pulmonary resistance is unsettled Lichtheim (12), as early as 1876, observed no appreciable change in the pressure in the small and large circulation, following the ligation of one pulmonary artery Similarly, Drinker, Churchill, and Ferry (9) recently demonstrated that, after occlusion of the left branch of the pulmonary artery, the right lung gives free passage to the pulmonary blood, even when cardiac inflow is greatly increased. On the other hand, after occlusion of the right branch of the pulmonary artery, a diminution in the aortic output appears at once It is, of course, questionable whether such acute experiments conducted in animals at rest under deep anesthesia bear at all on the significance of the "vascular reserve" of the lung, which, under exercise, may be essential and fully needed The presence of hypertrophy of the right ventricle in pulmonary emphysema is often cited as evidence for increased pulmonary resistance following obliteration of capillaries The significance of this observation is not as yet clear, for carefully analyzed autopsy material, showing the frequency and intensity of such changes in the cardiac muscle, is still lacking Conclusions from bedside or roentgenological observations are unsafe, because, as Stähelin (3) points out, the hearts of emphysematous patients tend to assume a transverse position and by x ray, may easily be mistaken for hypertrophied hearts Such was, indeed, the case in one of our patients in whom, as will be seen below, the orthodiagram showed enlargement and in whom the weight of the heart post mortem, was within normal limits Nevertheless, even if hypertrophy of the right ventricle does occur constantly in emphysema, it would not necessarily indicate increased pulmonary resistance. The muscular hypertrophy might be due to increased work in maintaining a high minute volume flow in an attempt to compensate for the insufficient ventilation

Venous pressure measurements might be expected to throw light, not only on the condition of the peripheral venous flow, but also on pressure relations within the thorax Were it not that these two factors may influence venous pressure in opposite directions, the significance of the venous pressure measurements would be greater

The significance of a diminished vital capacity in most patients with pulmonary emphysema is not clear Such a lowering may be due to pulmonary distention with loss of pulmonary elasticity, to chronic passive congestion, or to both While symptoms, such as weakness, cyanosis, and dyspnea appear in some patients with a diminished vital capacity, in others identical or more intense symptoms may be associated with a normal vital capacity It is, therefore, doubtful whether the clinical pathology of emphysema may be explained in every case on the basis of disturbed external ventilation

Measurements of the minute volume output of the heart would greatly aid our understanding of the circulation in emphysema Unfortunately, all methods available for such measurements postulate equilibrium between alveolar air and blood, the very relationship most seriously disturbed in this condition Dreser (13) and Beitzke (14) were aware of this difficulty According to them, the disturbance is due to change in the physical characteristics of the alveolar walls On the basis of theoretical considerations, studies of post mortem preparations, and experiments on glass models, they conclude that changes in the shape of the alveoli and infundibula interfere markedly with the diffusion of gases within the alveoli This disturbance, according to these authors, is of great importance Fortunately, an objective method for studying the velocity of blood flow through the lungs has been devised, which unlike the methods for studying the minute volume flow, does not depend upon gaseous equilibrium between blood and alveolar air Since previous observations have been concerned only indirectly with the dynamics of the circulation in pulmonary emphysema and since practically no direct measurements were available, the following investigation was undertaken

THE METHODS USED

Preceding studies (15) (16) have shown the feasibility of intravenous injection of radium C for the measurement of the "arm to arm circulation time" in normal subjects, as well as in patients with cardiovascular disease The method appeared particularly suited to the study of pulmonary emphysema, because, in contrast to minute volume methods, it neither postulates normal gaseous exchange nor requires cooperation on the part of the patients The "arm to arm circulation time," however, as pointed out previously, includes the arterial and venous blood flow times, and the pulmonary circulation time, the latter being of the greatest significance in emphysema

In order to measure the velocity of blood flow within the lesser circuit, the method used was that previously described (15) (16) This method measures, not only the pulmonary circulation time, but also, simultaneously, the velocity of venous flow from the elbow to the right auricle

All the measurements were obtained under basal metabolic conditions The pulse rate was counted several times before and after the test The venous pressure was measured according to the method of Moritz and Tabora All patients were in the hospital and so their clinical condition could be carefully studied

The abnormal physical signs, on which the diagnosis of emphysema was based, were barrel-shaped chest, low borders of the lungs, marked fixation of the thorax, obliteration of cardiac dulness, and limited excursion of the lower borders of the lungs The severity of emphysema in the patients varied considerably Some exhibited dyspnea and weakness only on exertion and a low vital capacity at rest. Other patients showed marked dyspnea, orthopnea, cyanosis, retraction of the lower ribs, and narrowing of the costal angle on inspiration (Hoover) (17) The etiological factors varied Some of the patients were suffering from long standing bronchial asthma, others from chronic bronchitis Some patients did not have any pulmonary infection, but, as a result of changes in the bony thorax and in the excursions of the lungs, had low vital capacities and clinical evidence of "ventilatory insufficiency" A short summary of the clinical findings of the patients is given below

RESULTS

Table 1 presents the findings in twenty-one of the twenty-five patients studied In these patients the velocity of blood flow was within normal limits The ages of these patients varied from twenty-five to seventy years although most of them were between forty and fifty years of age The clinical condition of patients in this group varied considerably Some complained of weakness and dyspnea only on exertion, others suffered from intense dyspnea and cyanosis at rest resulting in complete restriction of muscular activity Chronic bronchitis, bronchial asthma, and structural and functional changes in the thorax appeared to play a predominant

TABLE 1

Circulatory measurements in patients suffering from pulmonary emphysema, in whom the velocity of blood flow was within the limits of normal

Number of test	Date	Name	Diagnosis	Age	Temperature	Pulse	Surface area	Venous pressure	Arterial pressure		Vital capacity	Vital capacity per square meter	Injected	Circulation time			Circulation time per square meter		
									Systolic	Diastolic				Arm to heart	Pulmonary	Arm to arm	Arm to heart	Pulmonary	Arm to arm
							sq m	*cm H_2O*	*mm Hg*	*mm Hg*	*cc*	*cc*	*millicuries*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*
38	January 5, 1926	I B	Emphysema	41	97.2	63	1.62	1.2	110	74	2,600	1,540	5.1			22.0			13.0
39	January 5, 1926	I B	Emphysema	41	97.2	65	1.62	1.0	106	70	2,550	1,570	5.7			22.5			13.5
12	January 6, 1926	I B	Acute bronchitis, emphysema	25	97.8	57	1.77	1.8	92	40	3,500	1,920	7.3			18.0			10.0
13	January 6, 1926	I B	Acute bronchitis, emphysema	25	97.6	56	1.77	1.8	94	44	3,500	1,920	5.6			18.0			10.0
17	January 8, 1926	J G	Emphysema	37	98.0	64	1.67	−1.0	102	42	3,400	2,040	6.0			21.0			13.0
59	January 12, 1926	W D	Emphysema	27	98.2	44	1.41	3.2	112	56	2,200	1,560	3.1			20.0			14.0
73	February 10, 1926	D S	Chronic emphysema	45	98.2	68	1.92	1.4	124	82	3,450	1,790	2.0			16.0			8.3
79	February 10, 1926	J I	Chronic bronchitis, emphysema	44	100.0	95	1.36	0.0	94	54	1,700	1,250	5.2			19.0			13.9
97	February 17, 1926	C W	Bronchial asthma	29	97.8	68	1.55	4.5	112	72	3,950	2,550	0.9			17.0			10.9
111	February 27, 1926	A B	Emphysema	57	98.6	72	2.07	3.2	112	66	2,850	1,380	3.8			18.0			8.7
165	March 15, 1926	J D	Emphysema	53	98.2	61	2.19	2.2	168	108	3,450	1,560	3.4			21.0			9.6
171	March 17, 1926	F R	Chronic bronchitis, emphysema	31	98.4	105	1.59	4.5	135	68	1,750	1,100	3.7			17.0			10.6
175	March 17, 1926	L A	Chronic bronchitis, emphysema	25	97.8	84	1.56	−2.0	114	68	1,950	1,250	2.3			17.0			10.8

183	April 10, 1926	J D	Emphysema	40	98 2	52	2 19	−1 0	130	76	3,300	1 500	4 5			19 0			8 7
225	June 23, 1926	J S	Emphysema	38	98 6	68	1 68	2 5	130	76	3 350	2 000	4 8			18 0			10 7
235	September 1 1926	N U	Bronchial asthma	46		80					2 500		4 5	8 0	15 0	23 0			
270	October 21, 1926	M C	Emphysema	53	98 6	72	1 82	4 0	115	68	1 750	961	6 0	3 0	10 0	13 0	1 6	5 4	7 6
302	November 5, 1926	J K	Emphysema	40	98 0	70	1 74	6 5	144	74	3 400	1 954		3 5	13 0	16 5	2 0	7 5	9 5
323	December 7, 1926	T M	Chronic bronchitis asthma	44	98 6	70	1 72	3 5	112	72	4,825	2 805	4 0	4 0	10 0	14 0	2 3	5 8	8 1
345	January 18, 1927	F V	Emphysema	39	98 6	72	1 80	4 5	120	74	3 900	2 165	6 0	4 5	12 5	17 0	2 5	6 9	9 4
346	January 18 1927	V U	Emphysema	60	98 6	64	1 34	−2 5	114	64	1 100	821	7 0	9 0	15 0	24 0	6 7	11 2	17 9
379	February 23, 1927	J C	Emphysema	57	97 2	84	1 69	5 5	132	80	2 300	1 361	7 0	13 0	16 5	29 5	7 7	9 7	17 4
412	April 21, 1927	J M	Emphysema	52	97 2	92	1 50	−3 0	104	72	1 800	1 200	7 5	7 5	5 5	13 0	5 0	3 6	8 6
426	May 17, 1927	W S	Emphysema	70		78	1 63	−1 0	125	68	2,100	1 288		6 5	13 0	19 5	3 9	7 9	11 8
428	May 19, 1927	M. C	Emphysema	53		90	1 82	2 5	134	82	950	521	7 0	4 5	7 0	11 5	2 5	3 8	6 3

rôle in the etiology of emphysema in this group The normal or even increased velocity of blood flow, particularly in those patients who had many of the symptoms and signs of severe circulatory failure, such as conspicuous weakness, cyanosis, and dyspnea, is of great importance It shows that pulmonary emphysema alone is sufficient for the production of these symptoms and signs In some patients the velocity of blood flow was greater than that usually found in normal individuals As an example of the latter finding, we wish to call attention to the observations on M C (270, 428) This patient, as the appended summary of this clinical condition indicates, was suffering from severe emphysema and bronchial asthma of twenty-six years' duration Although his vital capacity was only 1750 cc (961 cc per square meter of body surface) at time of the first measurement, and 950 cc (521 cc per square meter) six months later at time of the second test, the crude pulmonary circulation time was 10 0 seconds on the first occasion, and 7 0 seconds at time of the second test when his general condition was worse

Severe pulmonary emphysema, therefore, does not necessarily obstruct the blood flow sufficiently to interfere with the normal velocity of blood flow On the contrary, in some patients increased speed of blood through the lungs may be present On the basis of the facts now available, one cannot say whether the normal or increased velocity observed in these patients is maintained with or without aid of the cardiac reserve Circulation and ventilation are closely related physiological mechanisms in the human body The significance of hyperventilation in compensating for circulatory failure is fully appreciated A reverse relation between circulation and ventilation possibly exists in what we may term "ventilatory failure" (emphysema)

With two exceptions, the vital capacities of the patients were moderately or greatly reduced The average vital capacity of twenty-five patients was 1583 cc per square meter of body surface (normal 2376 cc) This lowered vital capacity corresponds to that observed in patients who, as a result of arteriosclerotic heart disease with fibrillation of the auricles, complained of dyspnea but showed no congestive failure at the time of test

The average venous pressure of twenty-four patients of this group was 6 8 cm, which is slightly lower than 7 3 cm, the average venous pressure of sixty-five normal subjects

Comparison of the vital capacities with the symptoms and signs indicates no necessary correspondence between reduction in the vital capacity and the clinical condition of the patient If one considers that pulmonary emphysema is not a morphological or etiological entity, but is rather a state of "ventilatory insufficiency" due to faulty gaseous exchange, one easily understands this lack of parallelism We observed in a few patients, C W (97) and T M (323), normal, or even high, vital capacities with unmistakable clinical evidence of "ventilatory insufficiency" and without evidence of cardiac pathology It is in such patients, as Dresers (13) and Beitzke (14) point out, that the disturbance in gaseous exchange does not depend upon the impaired movement of the lungs or upon the diminution of air space, but rather upon physico-chemical characteristics of the alveolar wall which govern the diffusion of gases When one considers the numerous factors in the production of emphysema which vary in relative importance from case to case, there is no reason to expect a uniform correlation between the morphology of the lungs and the clinical condition of the patient This concept of pulmonary emphysema suggests that the degree of ventilatory insufficiency indicated by clinical symptoms and signs is associated with corresponding changes in the carbon-dioxide and oxygen content of the blood Such measurements in uncomplicated emphysema may possibly offer, therefore, a quantitative index of the degree of physiological disturbance manifested by these patients (18)

The venous pressures of patients of table 1 were within normal limits This finding indirectly confirms the fact that no severe failure of the right chambers of the heart was present.

Table 2 presents measurements on the four patients suffering from emphysema in whom the velocity of blood flow was slightly slower than normal. In patients in whom both the venous and the pulmonary blood flow were measured, the average time of the venous flow was 9 5 seconds, and, although these patients were completely disabled, the average velocity of blood flow through the lungs was only moderately prolonged (18 9 seconds) If we compare the average prolongation with that observed in patients suffering from cardiovascular disease, we find that the retardation of blood flow was less than that in patients with arteriosclerosis, who had never exhibited congestive failure and whose only complaint was dyspnea on exertion

While such slowing of the blood flow in patients with cardiovascular disease was associated with but slight restriction of muscular activity, the patients with pulmonary emphysema were completely incapacitated. The signal symptoms and signs shown by these patients are due, therefore, only to a slight extent to changes in the blood flow. Observations on J. C. (335) are of importance as we have had an opportunity to follow her condition closely and correlate our findings with post mortem examination. This patient suffered from the extreme form of the disease. The velocity of blood flow was measured only two months before her death, which was directly due to emphysema (see appended note, p. 569). She also showed myocardial failure, as judged from pitting edema around the ankles, but the crude pulmonary circulation time was only 19.5 seconds. The dyspnea, retraction of the lower ribs on inspiration, and the weakness cannot be explained on the basis of the retardation in blood flow. The fact that this patient practically choked to death with but slight slowing of the blood stream, and the fact that other patients with emphysema did not show marked slowing, suggests that with the defective aeration of blood due to ventilatory insufficiency such as is present in emphysema, conspicuous reduction in blood flow due to cardiac failure would probably be incompatible with life. This may also explain why elderly people with a tendency to emphysema and with cardiovascular disease show a more severe disturbance in bodily function than one would expect from the cardiovascular damage alone. This observation was mentioned in a previous communication.

The average vital capacity of patients in this group (table 2) was 1752 cc. (average of four measurements), or 812 cc. (average of two measurements) per square meter of body surface. This is a lower average than that observed in a group of cardiac patients with the most marked decompensation. The average of the venous pressures was 10.6 cm. This pressure is slightly higher than the average 7.3 cm., venous pressure of sixty-five normal subjects. The fact that most patients with marked pulmonary emphysema and with normal velocity of blood flow showed normal or slightly low venous pressures, and that others with slight prolongation of blood flow showed slightly increased venous pressures, indicates that pulmonary emphysema per se is not associated with increased venous pressure. If, there-

TABLE 2

Circulatory measurements on patients suffering from pulmonary emphysema, in whom the velocity of the blood flow was slowed

Number of test	Date	Name	Diagnosis	Age	Temperature	Pulse	Surface area	Venous pressure	Arterial pressure		Vital capacity	Vital capacity per square meter	Injected	Circulation time			Circulation time per square meter		
									Systolic	Diastolic				Arm to heart	Pulmonary	Arm to arm	Arm to heart	Pulmonary	Arm to arm
							sq. m.	*cm.* H_2O	*mm.* Hg	*mm.* Hg	*cc*	*cc*	*milli-curies*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*	*seconds*
236	September 1, 1926	J L	Bronchial asthma chronic emphysema	46	98 6	60		5 5	120	80	2,050		4 5	6 0	18 0	24 0			
237	September 2, 1926	J L.	Bronchial asthma chronic emphysema	46	98 6	72							10 0	12 0	19 0	31 0			
238	September 2, 1926	N U	Emphysema	46		84					2,500		4 5	9 0					
335	December 15, 1926	J C.	Emphysema	52	98 0	98	1 37	7 0	128	98	810	587	5 0	10 5	19 5	30 0	7 6	14 2	21·9
359	February 9, 1927	C H	Emphysema	54	98 0	84	1 59	4 5	100	66	1 650	1,037	8 0	10 0	19 0	29 0	6 3	11 9	18 2

fore, a patient with chronic pulmonary emphysema has a high venous pressure, cardiac pathology should in addition be suspected Because the clinical signs and symptoms of the patient may not aid in differentiating emphysema from myocardial failure, and furthermore, because emphysema and myocardial failure may be present in the same patient, in the estimation of the relative degree of pulmonary and cardiac disease, combined measurements of the vital capacity, venous pressure, and pulmonary blood flow may be of great diagnostic importance

SUMMARY AND CONCLUSIONS

1 Clinical studies and measurements of the velocity of blood flow, of the vital capacity of the lungs, and of the venous pressure are presented in twenty-five patients with pulmonary emphysema

2 The arm to arm and pulmonary circulation times were within normal limits in all but four patients

3 The vital capacity was definitely reduced in all but seven patients

4 The venous pressure was within normal limits in all patients

5 In the group of twenty-one patients in which the velocity of blood flow was within normal limits, the arm to arm circulation time averaged 18 6 seconds (normal, 17 5 seconds), the velocity of venous blood from the arm to the heart, 6 4 seconds (normal, 6 6 seconds), the crude pulmonary circulation time 11 8 seconds (normal, 10 8 seconds), and the actual pulmonary circulation time 7 6 seconds (normal 6 5 seconds) The vital capacities of this group averaged 1583 cc (normal, 2376 cc) per square meter of body surface, and the venous pressure, 6 8 cc of water (normal, 7 3 cm)

6 The observations reported demonstrate that even severe, chronic pulmonary emphysema does not necessarily obstruct the blood flow sufficiently to interfere with normal velocity of blood flow through the lungs On the contrary, in some patients with emphysema the velocity of blood flow is increased This increase in the velocity of blood flow through the lungs may be an effort on the part of the circulatory system to compensate for deficient ventilation, in which case it would be another expression of the close interrelation between the cardiovascular and ventilatory systems

7 Our investigation does not indicate whether the circulation in emphysema is maintained with or without aid of the cardiac reserve

8 In the group of four patients who showed a slightly retarded blood flow, the arm to arm circulation time averaged 28 5 seconds (normal, 17 5 seconds), the venous velocity time, 9 5 seconds (normal, 6 6 seconds), the crude pulmonary circulation time, 18 9 seconds (normal, 10.8 seconds), and the calculated actual pulmonary circulation time averaged 14 2 seconds (normal, 6 5 seconds) The average vital capacity was 1752 cc. or 812 cc per square meter of body surface (normal, 2376 cc per square meter), and the average venous pressure, 10 6 cm (normal, 7 3 cm)

9 Since our experience shows that in most patients with marked pulmonary emphysema, the venous pressure and the velocity of blood flow are normal, we believe that in the small group of four patients in which the blood flow was slightly retarded and the venous pressure elevated, pulmonary emphysema was complicated by circulatory failure

10 Clinical emphysema is not necessarily based on morphological changes in the lungs but is often a purely functional entity Hence, correlation between pathological findings and clinical signs and symptoms is not always to be expected

11 Because changes in the bony thorax, in the excursions of the lungs, or in the structure of the bronchi, bronchioles and alveoli may lead to identical functional consequences, and because analysis of the relative importance of these etiological factors is often difficult, we suggest, instead of emphysema, the term "ventilatory insufficiency" as a diagnostic group characteristic

12 In differentiating between "ventilatory" and cardiac insufficiency, and, when both are present, in evaluating their relative significance, combined measurements of the vital capacity, venous pressure, and the velocity of peripheral and pulmonary blood flow may be of great diagnostic importance

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APPENDIX

Abstracts of Histories and Physical Examinations of Patients with Pulmonary Emphysema

335 J C This patient s condition is given in greater detail because she manifested the extreme severity of pulmonary emphysema and because we were able to perform a post mortem examination She may serve therefore as an illustration of the extreme manifestation of the disease Ever since 1915 she had been suffering from increasing dyspnea. This was always present during exertion but showed marked fluctuation on different occasions As a child she suffered from empyema In 1919 she attended the Outpatient Department of the Massachusetts General Hospital where physical examination was normal except that respiratory sounds were diminished Occasional râles were heard The sputum was negative for tubercle bacilli X ray examination showed diffuse thickening of the lung markings extending outward from the roots Area of the right apex showed absence of lung markings

In 1920 she was admitted to the Boston City Hospital complaining of weakness and periodic attacks of dyspnea The chest was hyperresonant and the breath sounds were distant During this period an x ray picture of chest showed pneumothorax In 1925 fluoroscopic examination showed that both lung fields were extremely large The diaphragm was low and flat on both sides with practically no respiratory movement present Heart shadow was small Appearance was that of emphysema and pulmonary fibrosis

She was readmitted to the Boston City Hospital November 26, 1926, this time being forced to go to bed on account of weakness Her feet had become swollen during the preceding three weeks and there was marked dyspnea and orthopnea The face, lips and fingers were markedly cyanotic. The accessory respiratory muscles were active in respiration There was wheezing with markedly prolonged expiration The thorax was unusually long and narrow Level of diaphragm was very low and showed no excursion with interrupted deep breathing The chest was tympanitic and the respiratory sounds were distant. Scattered râles and rhonchi were heard particularly over the upper part of the chest The lower ribs and costal border line moved toward the median line with inspiration (positive Hoover's sign) The heart was 11.5 cm from the midline in the fifth intercostal space The sounds were distant There was slight pitting edema over both ankles While in the hospital patient showed considerable variations in intensity of dyspnea cyanosis and type of breathing The behavior of the lower ribs and the costal angle showed corresponding changes Digitalis did not produce definite improvement At time of test, the cyanosis was marked and dyspnea was intense and patient was able to recline even at 45° only for one or two minutes at a time

The specific gravity of the urine was 1010 to 1032 There was a slight trace of albumin The phthalein renal function test was 30 to 35 per cent in two hours

Blood pressure was 120 to 130—80 to 98 The Kahn blood test was repeatedly negative The blood urea nitrogen was 37 3 mg per 100 cc of blood The hemoglobin was 75 to 85 per cent Sputum was repeatedly negative for tubercle bacilli

FIG 1 GROSS POST-MORTEM APPEARANCE OF THE RIGHT LUNG IN PATIENT J C (No 335)

The surface of the lung is granular due to innumerable vesicles On the left margin several large blebs are visible

X-ray and fluoroscopic examination of the chest showed a low and flat diaphragm with slight movements only There was slight diffuse fibrosis throughout the lungs

Temperature 97 to 100°, pulse 80 to 100, respiration 20 to 25

Patient gradually grew weaker, the dyspnea and orthopnea increased, and she did not respond to medication On February 21 she died Except for the effect of morphine she was conscious to the end and she actually choked to death

The post mortem examination showed moderate pitting edema of the extremities The diaphragm was at the level of the seventh rib on the right The heart weighed 320 grams The chambers were moderately dilated Both lungs were unusually large, surface coarsely granular, consisting of small rounded elevations from 0 5 cm in diameter to 2 cm and raised about 0 4 cm Their color ranged from pearly to purple On palpation the elevations were found to be thin walled, air-containing vesicles, which also contained a certain amount of fluid, so that the lungs were extremely crepitant On section the lung was an even dark red, exuding a large amount of bloody fluid The cut surface presented the cross section of tremendously dilated, or ruptured and confluent, alveoli There was a small amount of mucus in the bronchi but no definite purulent exudate On the right the interlobar space between the upper and middle lobes was obliterated by fine fibrous adhesions The rest of the findings were unessential. Anatomical diagnosis emphysema of lungs, congestion of lungs, passive congestion of liver, old pleuritis and pericarditis, edema

38–39 L B has suffered from cough and repeated attacks of "asthma" for twenty six years He had pneumonia nine years ago He is unable to do hard labor but is troubled with dyspnea only during the asthmatic attacks The chest is barrel-shaped, the absolute cardiac dulness is obliterated The level of the diaphragm changes only 1 5 cm with deep inspiration The heart sounds are distant. Diagnosis chronic bronchitis chronic bronchial asthma, pulmonary emphysema

42–43 F B complains of cough, shortness of breath and "choked sensation" on slight exertion He is unable to do hard labor The thorax is fixed. The anteroposterior diameter is unusually long Numerous rhonchi are heard over the chest Heart is normal. The brachial arteries are slightly thickened Diagnosis chronic bronchitis, pulmonary emphysema

47 F G has suffered from cough and weakness for years The chest is markedly pigeon-shaped, with unusually long anteroposterior diameter The absolute cardiac dulness is completely obliterated Musical rhonchi are heard over the chest There is a very slight excursion of the diaphragm on deep inspiration The heart is normal Diagnosis chronic bronchitis, pulmonary emphysema

73 D S has suffered from repeated attacks of cough with productive expectoration for five to ten years During the past year there has been increasing dyspnea Patient was dyspneic at the time of test The thorax did not move with respiration and the costal angle was very wide Expiration was markedly prolonged Rhonchi and râles were heard over both bases The heart was normal Diagnosis chronic bronchitis, emphysema

79 F L complains of dyspnea on moderate exertion and of chronic cough.

Heart is normal and orthodiagram does not reveal enlargement of the cardiac shadow Diagnosis chronic bronchitis, pulmonary emphysema

379 J C has suffered from increasing dyspnea for the past 5 years He has been coughing for two years The chest is barrel-shaped and does not show excursion with respiration The absolute cardiac dulness is obliterated The level of the diaphragm is 8 cm below angle of scapula and moves 3 cm down after a long inspiration Diagnosis chronic bronchitis, pulmonary emphysema

412 J M suffered from pneumonia 4 years ago He stayed in bed for 3 months at that time and has felt weak since, so much so, that he was considered by a physician as a patient suffering from heart disease He has had a cough for the past three and a half years and for the past two years has been unable to work As soon as he lifts anything heavy he becomes "choked" and short-winded There is a bluish lividity over the lips and face The neck is short and the respiration labored Thorax is short with a long anteroposterior diameter The absolute cardiac dulness is obliterated Breath sounds are suppressed Squeaks are heard over the posterior aspect of the chest Diagnosis pulmonary emphysema

236, 237 J L is suffering from attacks of asthma which he has had for the last 11 years For the last 2 years he has been unable to do hard work The past month he has been unable to do any work whatever The lips are cyanotic The anteroposterior diameter of the chest is increased Thorax is hyperresonant and the movements of the diaphragm are but slight on deep inspiration Many coarse, squeaking and sibilant râles are heard Diagnosis bronchial asthma, chronic bronchitis, pulmonary emphysema

359 C H has been suffering from cough and frequent attacks of asthma for 5 years He has felt so weak during the past 2 years that he has been unable to work At time of test he was suffering from orthopnea and dyspnea and felt so weak that he was unable to walk The chest was flat and long and hyper-resonant The absolute cardiac dulness was obliterated The excursion of the diaphragm was but slight (Hoover's sign absent) Diagnosis bronchial asthma, pulmonary emphysema

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